

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
29 January 2004 (29.01.2004)

PCT

(10) International Publication Number  
**WO 2004/009560 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 239/30**,  
239/48, 239/42, 239/36, A61K 31/505, A61P 29/02

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(21) International Application Number:  
PCT/TB2003/002879

(22) International Filing Date: 21 July 2003 (21.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
548/MAS/2002 22 July 2002 (22.07.2002) IN

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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**Declaration under Rule 4.17:**

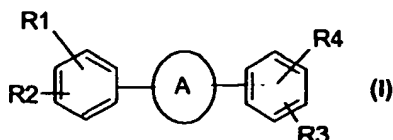
— *of inventorship (Rule 4.17(iv)) for US only*

**Published:**

— *with international search report*  
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: NOVEL BIO-ACTIVE MOLECULES



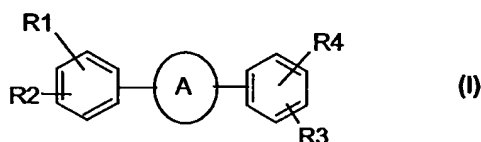
(57) Abstract: The present invention relates to novel derivatives of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts and pharmaceutically acceptable compositions containing them. The present invention more particularly provides novel pyrimidine derivatives of the general formula (I).

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## NOVEL BIO-ACTIVE MOLECULES

### Field of the Invention

The present invention relates to novel compounds of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts and pharmaceutically acceptable compositions containing them. The present invention more particularly provides novel pyrimidine derivatives of the general formula (I).



The present invention also provides a process for the preparation of the above said novel compounds of the formula (I) pharmaceutically acceptable salts, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them.

The novel compounds of the present invention are useful for the treatment of inflammation and immunological diseases. Particularly the compounds of the present invention are useful for the treatment of inflammation and immunological diseases those mediated by cytokines such as TNF- $\alpha$ , IL-1, IL-6, IL-1 $\beta$ , IL-8 and cyclooxygenase such as COX-1, COX-2 and COX-3. The compounds of the present invention are also useful for the treatment of rheumatoid arthritis; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; ischemic heart disease, atherosclerosis, cancer, ischemic-induced cell damage, pancreatic  $\beta$  cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis;

anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever and myalgias due to infection; and diseases mediated by HIV-1; HIV-2; HIV-3; cytomegalovirus (CMV); influenza; adenovirus; the herpes viruses (including HSV-1, HSV-2) and herpes zoster viruses.

### **Background of Invention**

It has been reported that Cyclooxygenase enzyme exists in three isoforms, namely, COX-1, COX-2 and COX-3. COX-1 enzyme is essential and primarily responsible for the regulation of gastric fluids whereas COX-2 enzyme is present at the basal levels and is reported to have a major role in the prostaglandin synthesis for inflammatory response. These prostaglandins are known to cause inflammation in the body. Hence, if the synthesis of these prostaglandins is stopped by way of inhibiting COX-2 enzyme, inflammation and its related disorders can be treated. COX-3 possesses glycosylation-dependent cyclooxygenase activity. Comparison of canine COX-3 activity with murine COX-1 and COX-2 demonstrated that this enzyme is selectively inhibited by analgesic/antipyretic drugs such as acetaminophen, phenacetin, antipyrine, and dipyrrone, and is potently inhibited by some nonsteroidal antiinflammatory drugs. Thus, inhibition of COX-3 could represent a primary central mechanism by which these drugs decrease pain and possibly fever. Recent reports show that inhibitors of COX-1 enzyme causes gastric ulcers, where as selective COX-2 and COX-3 enzyme inhibitors are devoid of this function and hence are found to be safe.

The present invention is concerned with treatment of immunological diseases or inflammation, notably such diseases are mediated by cytokines or cyclooxygenase. The principal elements of the immune system are macrophages

or antigen-presenting cells, T cells and B cells. The role of other immune cells such as NK cells, basophils, mast cells and dendritic cells are known, but their role in primary immunologic disorders is uncertain. Macrophages are important mediators of both inflammation and providing the necessary "help" for T cell stimulation and proliferation. Most importantly macrophages make IL-1, IL-12 and TNF- $\alpha$  all of which are potent pro-inflammatory molecules and also provide help for T cells. In addition, activation of macrophages results in the induction of enzymes, such as cyclooxygenase-2 (COX-2) and cyclooxygenase-3 (COX-3), inducible nitric oxide synthase (iNOS) and production of free radicals capable of damaging normal cells. Many factors activate macrophages, including bacterial products, superantigens and interferon gamma (IFN  $\gamma$ ). It is believed that phosphotyrosine kinases (PTKs) and other undefined cellular kinases are involved in the activation process.

Cytokines are molecules secreted by immune cells that are important in mediating immune responses. Cytokine production may lead to the secretion of other cytokines, altered cellular function, cell division or differentiation. Inflammation is the body's normal response to injury or infection. However, in inflammatory diseases such as rheumatoid arthritis, pathologic inflammatory processes can lead to morbidity and mortality. The cytokine tumor necrosis factor-alpha (TNF- $\alpha$ ) plays a central role in the inflammatory response and has been targeted as a point of intervention in inflammatory disease. TNF- $\alpha$  is a polypeptide hormone released by activated macrophages and other cells. At low concentrations, TNF- $\alpha$  participates in the protective inflammatory response by activating leukocytes and promoting their migration to extravascular sites of inflammation (Moser et al., J.Clin.Invest., 83, 444-55, 1989). At higher concentrations, TNF- $\alpha$  can act as a potent pyrogen and induce the production of other pro-inflammatory cytokines (Haworth et al., Eur.J.Immunol., 21, 2575-79,

1991; Brennan *et al.*, Lancet, 2, 244-7, 1989). TNF- $\alpha$  also stimulates the synthesis of acute-phase proteins. In rheumatoid arthritis, a chronic and progressive inflammatory disease affecting about 1% of the adult U.S. population, TNF- $\alpha$  mediates the cytokine cascade that leads to joint damage and destruction (Arend *et al.*, Arthritis Rheum., 38, 151-60, 1995). Inhibitors of TNF- $\alpha$ , including soluble TNF receptors (etanercept) (Goldenberg, Clin Ther., 21, 75-87, 1999) and anti-TNF- $\alpha$  antibody (infliximab) (Luong *et al.*, Ann Pharmacother., 34, 743-60, 2000), have recently been approved by the U.S. Food and Drug Administration (FDA) as agents for the treatment of rheumatoid arthritis.

Elevated levels of TNF- $\alpha$  have also been implicated in many other disorders and disease conditions, including cachexia, septic shock syndrome, osteoarthritis, inflammatory bowel disease such as Crohn's disease and ulcerative colitis etc.

Elevated levels of TNF- $\alpha$  and/or IL-1 over basal levels have been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic  $\beta$  cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection. HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), and herpes zoster are also exacerbated by TNF- $\alpha$ .

It can be seen that inhibitors of TNF- $\alpha$  are potentially useful in the treatment of a wide variety of diseases. Compounds that inhibit TNF- $\alpha$  have been described in several patents.

Excessive production of IL-6 is implicated in several disease states, it is highly desirable to develop compounds that inhibit IL-6 secretion. Compounds that inhibit IL-6 have been described in U.S. Pat. Nos. 6,004,813; 5,527,546 and 5,166,137.

The cytokine IL-1 $\beta$  also participates in the inflammatory response. It stimulates thymocyte proliferation, fibroblast growth factor activity, and the release of prostaglandin from synovial cells. Elevated or unregulated levels of the cytokine IL-1 $\beta$  have been associated with a number of inflammatory diseases and other disease states, including but not limited to adult respiratory distress syndrome, allergy, Alzheimer's disease etc. Since overproduction of IL-1 $\beta$  is associated with numerous disease conditions, it is desirable to develop compounds that inhibit the production or activity of IL-1 $\beta$ .

In rheumatoid arthritis models in animals, multiple intra-articular injections of IL-1 have led to an acute and destructive form of arthritis (Chandrasekhar et al., *Clinical Immunol Immunopathol.*, 55, 382, 1990). In studies using cultured rheumatoid synovial cells, IL-1 is a more potent inducer of stromelysin than TNF- $\alpha$ . (Firestein, *Am. J. Pathol.*, 140, 1309, 1992). At sites of local injection, neutrophil, lymphocyte, and monocyte emigration has been observed. The emigration is attributed to the induction of chemokines (e.g., IL-8), and the up-regulation of adhesion molecules (Dinarello, *Eur. Cytokine Net.*, 5, 517-531, 1994).

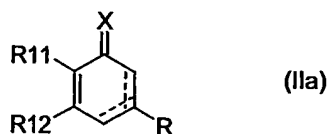
In rheumatoid arthritis, both IL-1 and TNF- $\alpha$  induce synoviocytes and chondrocytes to produce collagenase and neutral proteases, which leads to tissue

destruction within the arthritic joints. In a model of arthritis (collagen-induced arthritis (CIA) in rats and mice) intra-articular administration of TNF- $\alpha$  either prior to or after the induction of CIA led to an accelerated onset of arthritis and a more severe course of the disease (Brahm et al., Lymphokine Cytokine Res., 11, 253, 1992; and Cooper, Clin. Exp. Immunol., 898, 244, 1992).

IL-8 has been implicated in exacerbating and/or causing many disease states in which massive neutrophil infiltration into sites of inflammation or injury (e.g., ischemia) is mediated chemotactic nature of IL-8, including, but not limited to, the following: asthma, inflammatory bowel disease, psoriasis, adult respiratory distress syndrome, cardiac and renal reperfusion injury, thrombosis and glomerulonephritis. In addition to the chemotaxis effect on neutrophils, IL-8 has also has ability to activate neutrophils. Thus, reduction in IL-8 levels may lead to diminished neutrophil infiltration.

Few prior art reference which disclose the closest pyrimidine compounds are given here:

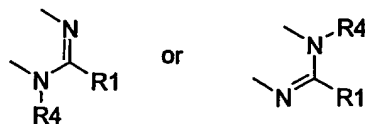
- i) US patent Nos. 6,420,385 discloses novel compounds of formula (IIa)



wherein

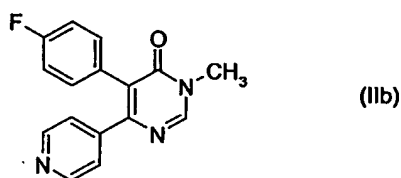


represents

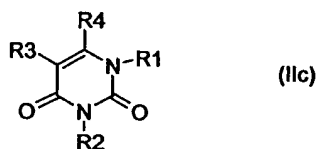


X is O, S or NR<sub>5</sub>; R<sub>1</sub> and R<sub>2</sub> each independently represent --Y or --Z--Y, and R<sub>3</sub> and R<sub>4</sub> each independently --Z--Y or R<sub>3</sub> is a hydrogen radical; provided that R<sub>4</sub> is other than a substituted-aryl, (substituted-aryl)methyl or (substituted-aryl)ethyl radical; wherein each Z is independently optionally substituted alkyl, alkenyl, alkynyl, heterocyclyl, aryl or heteroaryl; Y is independently a hydrogen; halo, cyano, nitro, etc., R<sub>5</sub> is independently a hydrogen, optionally substituted alkyl, alkenyl, alkynyl etc., R<sub>11</sub> and R<sub>12</sub> are each independently represent optionally substituted aryl or heteroaryl.

An example of these compounds is shown in formula (IIb)

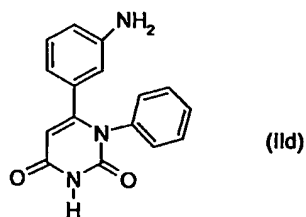


ii) DE 2142317 discloses hypnotic uracil derivatives of formula (IIc)



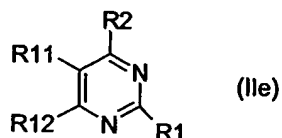
wherein R<sub>1</sub> is H, alkyl, alkenyl, dialkylaminoalkyl, or aralkyl; R<sub>2</sub> is H, alkyl, aryl, or halogen; R<sub>3</sub> is alkyl, alkenyl, cycloalkyl, aralkyl, aralkenyl, or aryl, R<sub>4</sub> is alkyl, alkenyl, cycloalkyl, aralkyl, aryl, etc.

An example of these compounds is shown in formula (IIId)



iii) US patent Nos. 6,420,385 and 6,410,729 discloses novel compounds of formula (IIe)





wherein  $R_1$  and  $R_2$  are each independently -Z-Y, preferably,  $R_2$  is a radical of hydrogen,  $C_1$ - $C_4$  alkyl, halo, hydroxy, amino, etc., Z is independently a bond, alkyl, alkenyl etc., Y is independently a hydrogen radical, halo, nitro radical;  $R_{20}$  is independently (1) alkyl, alkenyl, heterocyclyl radical, aryl, heteroaryl;  $R_{21}$  is independently hydrogen radical,  $R_{20}$ ;  $R_{22}$  is independently hydrogen, heterocyclyl, aryl or heteroaryl

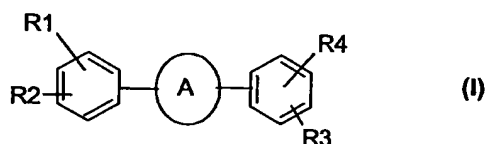
### Objective of the Invention

We have focused our research to identify selective COX-1, COX-2 and COX-3 inhibitors, which are devoid of any side effects normally associated with anti-inflammatory agents. Our sustained efforts have resulted in novel compounds of the formula (I). The derivatives may be useful in the treatment of inflammation and immunological diseases. Particularly the compound of the present invention are useful for the treatment of inflammation and immunological diseases those mediated by cytokines such as  $TNF-\alpha$ , IL-1, IL-6, IL-1 $\beta$ , IL-8 and cyclooxygenase such as COX-1, COX-2 and COX-3. The compound of the present invention are also useful for the treatment of rheumatoid arthritis; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; ischemic heart disease; atherosclerosis; cancer; ischemic-induced cell damage; pancreatic  $\beta$  cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury;

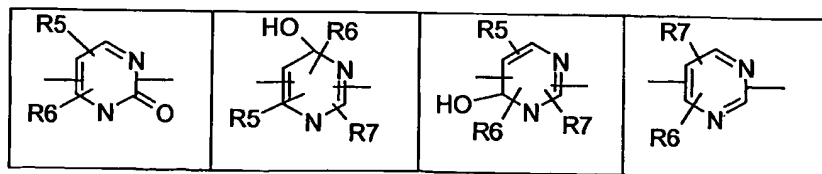
atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection; and diseases mediated by HIV-1; HIV-2; HIV-3; cytomegalovirus (CMV); influenza; adenovirus; the herpes viruses (including HSV-1, HSV-2) and herpes zoster viruses.

### Summary of the Invention

The present invention relates to novel pyrimidine derivatives of the formula (I)



their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> may be same or different and independently represent hydrogen, hydroxy, nitro, nitroso, formyl, azido, halo or substituted or unsubstituted groups selected from alkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; A represents pyrimidine derivative of the formula



wherein R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, may be same or different and represent, hydrogen, nitro, nitroso, formyl, azido, halo, or substituted or unsubstituted groups selected from

alkyl, alkoxy, acyl, cycloalkyl, haloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; the pyrimidine group may be attached to the phenyl through carbon or nitrogen atom.

### Detailed Description of the Invention

Suitable groups represented by  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ , are selected from hydrogen, hydroxy, nitro, nitroso, formyl, azido, halogen atom such as fluorine, chlorine, bromine or iodine; or substituted or unsubstituted linear or branched ( $C_1$ - $C_6$ ) alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; haloalkyl such as chloromethyl, chloroethyl, trifluoromethyl, trifluoroethyl, dichloromethyl, dichloroethyl and the like, which may be substituted; aryl group such as phenyl or naphthyl, the aryl group may be substituted; cyclo ( $C_3$ - $C_6$ ) alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; acyl group such as  $-C(=O)CH_3$ ,  $-C(=O)C_2H_5$ ,  $-C(=O)C_3H_7$ ,  $-C(=O)C_6H_{13}$ ,  $-C(=S)CH_3$ ,  $-C(=S)C_2H_5$ ,  $-C(=S)C_3H_7$ ,  $-C(=S)C_6H_{13}$ , benzoyl and the like, which may be substituted; linear or branched ( $C_1$ - $C_6$ ) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; aryloxy group such as phenoxy, naphthoxy, the aryloxy group may be substituted; aralkoxy group such as benzyloxy, phenethyloxy and the like, which may be substituted; acyloxy group such as  $MeCOO-$ ,  $EtCOO-$ ,  $PhCOO-$  and the like, which may be substituted; heterocyclyl groups such as pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, and the like, the heterocyclyl group may be substituted; heteroaryl group may be mono or fused system such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyrazine, piperazine, benzopyranyl, benzofuranyl, benzimidazolyl,

benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiaazolyl and the like, the heteroaryl group may be substituted; aralkyl group such as benzyl, phenylethyl, phenyl propyl and the like, which may be substituted; amino, which may be substituted; hydrazine, which may be substituted; monoalkylamino group such as  $\text{-NHCH}_3$ ,  $\text{-NHC}_2\text{H}_5$ ,  $\text{-NHC}_3\text{H}_7$ ,  $\text{-NHC}_6\text{H}_{13}$ , and the like, which may be substituted; dialkylamino group such as  $\text{-N(CH}_3)_2$ ,  $\text{-NCH}_3(\text{C}_2\text{H}_5)$ ,  $\text{-N(C}_2\text{H}_5)_2$  and the like, which may be substituted; acylamino group such as  $\text{-NHC(=O)CH}_3$ ,  $\text{-NHC(=O)C}_2\text{H}_5$ ,  $\text{-NHC(=O)C}_3\text{H}_7$ ,  $\text{-NHC(=O)C}_6\text{H}_{13}$ , and the like, which may be substituted; alkoxy carbonyl group such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and the like, the alkoxy carbonyl group may be substituted; aryloxy carbonyl group such as phenoxycarbonyl, naphthoxycarbonyl, the aryloxy carbonyl group may be substituted; alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl and the like, the alkylsulfonyl group may be substituted; arylsulfonyl group such as phenylsulfonyl or naphthylsulfonyl, the arylsulfonyl group may be substituted; alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, iso-propylsulfinyl and the like, the alkylsulfinyl group may be substituted; arylsulfinyl group such as phenylsulfinyl or naphthylsulfinyl, the arylsulfinyl group may be substituted; alkylthio group such as methylthio, ethylthio, n-propylthio, iso-propylthio and the like, the alkylthio group may be substituted; arylthio group such as phenylthio, or naphthylthio, the arylthio group may be substituted; alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, which may be substituted; sulfamoyl; carboxylic acid or its derivatives such as esters, amides and acid halides.

Suitable groups represented by  $\text{R}_5$ ,  $\text{R}_6$  and  $\text{R}_7$  are selected from hydrogen, nitro, nitroso, formyl, azido, halo; substituted or unsubstituted linear or branched

(C<sub>1</sub>-C<sub>6</sub>) alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; linear or branched (C<sub>1</sub>-C<sub>6</sub>) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; acyl group such as -C(=O)CH<sub>3</sub>, -C(=O)C<sub>2</sub>H<sub>5</sub>, -C(=O)C<sub>3</sub>H<sub>7</sub>, -C(=O)C<sub>6</sub>H<sub>13</sub>, -C(=S)CH<sub>3</sub>, -C(=S)C<sub>2</sub>H<sub>5</sub>, -C(=S)C<sub>3</sub>H<sub>7</sub>, -C(=S)C<sub>6</sub>H<sub>13</sub>, benzoyl and the like, which may be substituted; cyclo (C<sub>3</sub>-C<sub>6</sub>) alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; haloalkyl such as chloromethyl, chloroethyl, trifluoromethyl, trifluoroethyl, dichloromethyl, dichloroethyl and the like, which may be substituted; amino, which may be substituted; hydrazine, which may be substituted; alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, which may be substituted; monoalkylamino group such as -NHCH<sub>3</sub>, -NHC<sub>2</sub>H<sub>5</sub>, -NHC<sub>3</sub>H<sub>7</sub>, -NHC<sub>6</sub>H<sub>13</sub>, and the like, which may be substituted; dialkylamino group such as -N(CH<sub>3</sub>)<sub>2</sub>, -NCH<sub>3</sub>(C<sub>2</sub>H<sub>5</sub>), -N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub> and the like, which may be substituted; acylamino group such as -NHC(=O)CH<sub>3</sub>, -NHC(=O)C<sub>2</sub>H<sub>5</sub>, -NHC(=O)C<sub>3</sub>H<sub>7</sub>, -NHC(=O)C<sub>6</sub>H<sub>13</sub>, and the like, which may be substituted; alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl and the like, the alkylsulfonyl group may be substituted; arylsulfonyl group such as phenylsulfonyl or naphthylsulfonyl, the arylsulfonyl group may be substituted; alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, iso-propylsulfinyl and the like, the alkylsulfinyl group may be substituted; arylsulfinyl group such as phenylsulfinyl or naphthylsulfinyl, the arylsulfinyl group may be substituted; alkylthio group such as methylthio, ethylthio, n-propylthio, iso-propylthio and the like, the alkylthio group may be substituted; arylthio group such as phenylthio, or naphthylthio, the arylthio group may be substituted; aryloxycarbonyl group such as phenoxycarbonyl, naphthoxycarbonyl, the aryloxycarbonyl group may be

substituted; alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and the like, the alkoxycarbonyl group may be substituted; sulfamoyl; carboxylic acid or its derivatives such as esters, amides and acid halides.

When the groups  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$  and  $R_7$  are substituted, the substituents may be selected from halogen, hydroxy, nitro, cyano, azido, nitroso, amino, hydrazine, formyl, alkyl, aryl, cycloalkyl, alkoxy, aryloxy, acyl, acyloxyacyl, heterocyclyl, heteroaryl, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, sulfamoyl, alkoxyalkyl groups or carboxylic acids or its derivatives and these substituents are as defined above.

Pharmaceutically acceptable salts of the present invention include alkali metal like Li, Na, and K, alkaline earth metal like Ca and Mg, salts of organic bases such as diethanolamine,  $\alpha$ -phenylethylamine, benzylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. Salts also include amino acid salts such as glycine, alanine, cystine, cysteine, lysine, arginine, phenylalanine, guanidine etc. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, tosylates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of crystallization such as alcohols.

Representative compounds according to the present invention include:

4-Chloro-5,6-diphenyl-2-(trifluoromethyl)pyrimidine;

4-Chloro-6-(4-methylphenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine;

4-Chloro-6-(4-fluorophenyl)-5-phenyl-2-(trifluoromethyl) pyrimidine;  
4-Chloro-6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidine;  
4-Chloro-5-(4-chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine;  
4-Chloro-5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine;  
2,4-Dichloro-5,6-diphenylpyrimidine;  
2,4-Dichloro-6-(4-methylphenyl)-5-phenylpyrimidine;  
6-(4-Chlorophenyl)-2,4-dichloro-5-phenylpyrimidine;  
5-(4-Chlorophenyl)-2,4-dichloro-6-phenylpyrimidine;  
2,4-Dichloro-5-(4-methoxyphenyl)-6-phenylpyrimidine;  
2,4-Dichloro-5-[4-(methylthio)phenyl]-6-phenylpyrimidine;  
2,4-Dichloro-6-(4-chlorophenyl)-5-[4-(methylthio)phenyl] pyrimidine;  
2,4-Dichloro-5-(4-chlorophenyl)-6-(4-methylphenyl)pyrimidine;  
4-Azido-5,6-diphenyl-2-(trifluoromethyl)pyrimidine;  
4-Azido-6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidine;  
4-Azido-5-(4-chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine;  
4-Azido-5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine;  
2,4-Diazido-5,6-diphenylpyrimidine;  
2,4-Diazido-5-(4-chlorophenyl)-6-phenylpyrimidine;  
4-Hydrazino-5,6-diphenyl-2-(trifluoromethyl)pyrimidine;  
4-Hydrazino-6-(4-methylphenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine;  
4-Hydrazino-6-(4-fluorophenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine;  
4-Hydrazino-6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidine;

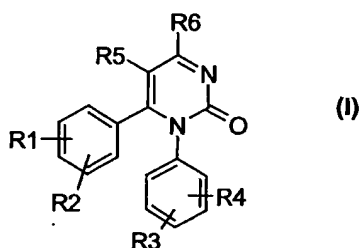
5-(4-Chlorophenyl)-4-hydrazino-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine;  
5-(4-Fluorophenyl)-4-hydrazino-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine;  
2-Chloro-5,6-diphenyl-4-hydrazinopyrimidine;  
2-Chloro-4-hydrazino-5-[4-(methylthio)phenyl]-6-phenylpyrimidine;  
2,4-Dihydrazino-5,6-diphenylpyrimidine;  
2,4-Dihydrazino-5-[4-(methylthio)phenyl]-6-phenylpyrimidine;  
N'-[5,6-Diphenyl-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide;  
N'-[6-(4-Methylphenyl)-5-phenyl-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide;  
N'-[6-(4-Fluorophenyl)-5-phenyl-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide;  
N'-[6-[4-(Methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide;  
N'-[5-(4-Chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide;  
N'-[5-(6-Fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide;  
N'-[5-(4-Chlorophenyl)-[6-(4-methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidin-4-yl]trifluoroacetohydrazide;  
4-Chloro-1,6-diphenylpyrimidine-2(1H)-one;  
4-Azido-6-[(4-methylthio)phenyl]-1-phenylpyrimidin-2(1H)-one;  
4-[3-(4-Chlorophenyl)-2-oxo-6-trifluoromethyl-2,3-dihydro-pyrimidin-4-yl]benzenesulfonamide;  
6-[(4-Methylsulfonyl)phenyl]-1-p-tolyl-4-(trifluoromethyl)pyrimidin-2(1H)-one;  
4-Azido-6-[(4-methylsulfonyl)phenyl]-1-p-tolyl-pyrimidin-2(1H)-one;



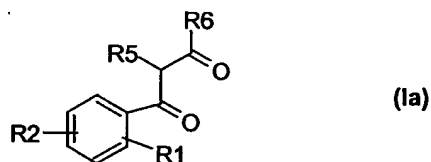
- 1 4-(6-Azido-3-methoxyphenyl-2-oxo-2,3-dihydropyrimidin-4-yl)benzenesulfonamide;
- 2 4-(6-Azido-4-methoxyphenyl-2-oxo-2,3-dihydropyrimidin-4-yl)benzenesulfonamide;
- 1 2-Chloro-5-(4-chlorophenyl)-4-methylthio-6-[(4-methylthio)phenyl]pyrimidine;
- 6-[(4-Methylthio)phenyl]-1-phenyl-4-(trifluoromethyl)pyrimidin-2(1H)-one;
- 1 4-(2-Oxo-3-phenyl-6-trifluoromethyl-2,3-dihydropyrimidin-4-yl)benzenesulfonamide;
- 9 4-Methylthio-5,6-bis(p-tolyl)pyrimidine;
- 4-Methylthio-5,6-diphenyl-pyrimidin-2-ol;
- 1 1 4-Methylsulfonyl-5,6-bis(p-tolyl)pyrimidine;
- 1,6-Diphenyl-4-(trifluoromethyl)pyrimidin-2(1H)-one;
- 1 3 4-(2-Hydroxy-6-methylthio-5-phenylpyrimidin-4-yl)benzenesulfonamide;
- 14 4-Methylthio-6-[(4-methylthio)phenyl]-5-phenylpyrimidine;
- 2-Chloro-4-methylthio-5,6-bis(p-tolyl)pyrimidine;
- 2-Chloro-4-methylthio-6-[(4-methylthio)phenyl]-5-p-tolyl-pyrimidine;
- 5-(4-Bromophenyl)-2-chloro-4-methylthio-6-[(4-methylthio)phenyl]pyrimidine;
- 1 5 5-(2-Bromophenyl)-4-methylthio-6-[(4-methylthio)phenyl]pyrimidin-2-ol;
- 4-(2-Chloro-6-methylthio-5-phenylpyrimidin-4-yl)benzenesulfonamide;
- 2-Chloro-4,5-bis-(4-methoxyphenyl)-6-(methylthio)pyrimidine;
- 2-Chloro-4-methylthio-6-[(4-methylthio)phenyl]-5-phenylpyrimidine;
- 2,4-Diazido-6[(4-methylthio)phenyl]-5-phenylpyrimidine;
- 2,4-Diazido-5-(4-bromophenyl)-6-(4-methylthiophenyl)pyrimidine;
- 4-Chloro-6-[(4-methylsulfonyl)phenyl]-1-phenylpyrimidin-2(1H)-one;
- 4-Azido-1-(2-fluorophenyl)-6-[(4-methylthio)phenyl]-pyrimidin-2(1H)-one;
- 2-[(4-Methylsulfonyl)phenyl]-6-trifluoromethyl-3-[(4-trifluoromethyl)phenyl]-3,4-dihydropyrimidin-4-ol;

5-(3-Fluorophenyl)-4-methylthio-6-[(4-methylthio)phenyl]pyrimidin-2-ol and  
4-(6-Hydroxy-6-methyl-2-p-tolyl-4-trifluoromethyl-6H-pyrimidin-1-yl)benzenesulfonamide.

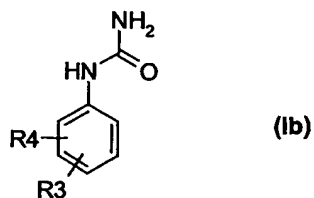
According to another embodiment of the present invention, there is provided a process for the preparation of novel compounds of the formula (I)



where all symbols are as defined earlier may be prepared by a process which comprises condensing a compound of formula (Ia)



wherein all symbols are as defined earlier with a compound of the formula (Ib)

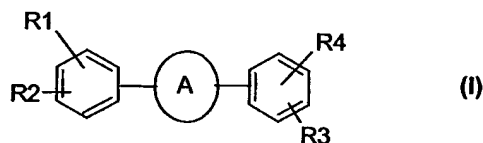


where all symbols are as defined above.

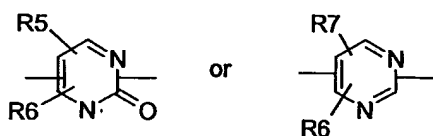
The reaction of compound of formula (Ia) with compound of formula (Ib) may be carried out using appropriate solvents like toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetone, ethylacetate, acetonitrile, N,N-dimethylformamide,

dimethylsulfoxide, ethanol, methanol, isopropylalcohol, tert-butylalcohol, acetic acid, propionic acid etc., a mixture thereof or the like. The condensation reaction is carried out in acidic condition using mineral or organic acids, or basic conditions viz. carbonates, bicarbonates, hydrides, hydroxides, alkyls and alkoxides of alkali metals and alkaline earth metals or by neat reaction. The reaction is carried out using phase transfer catalysts viz. triethylbenzylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium hydrogensulphate, tricaprylmethylammonium chloride (aliquat 336) and the like. The reaction is usually carried out under cooling to refluxing conditions. The final product purified by using chromatographic techniques or by recrystallization.

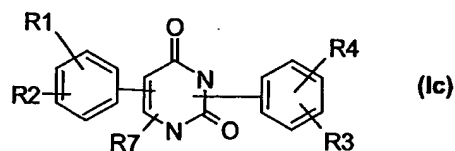
According to another embodiment of the present invention, there is provided a process for the preparation of novel compounds of the formula (I)



where A represents



wherein  $R^6$  represents halogen atom,  $R^5$  and  $R^7$  are as defined above may be prepared by converting the compound of formula (Ic)

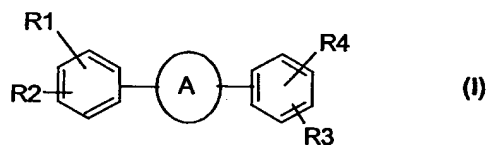


wherein all symbols are as defined earlier.

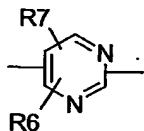
The compound of formula (Ic) is prepared according to the procedure described in our PCT application Nos. PCT/IB03/01287 and PCT/IB03/01289.

The conversion of compound of formula (Ic) is carried out using reagents such as phosphorus oxychloride, thionyl chloride, phosphorus trichloride, phosphorus pentachloride, oxalyl chloride and the like in the presence or absence of solvents such as toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, diphenyl ether and the like or a mixture thereof, in presence or absence of dimethylformamide, N,N-dimethylaniline, N,N-diethylaniline and the like. The reaction is carried out at a temperature in the range of 20 °C to reflux temperatures for a period in the range of 2 to 12 h.

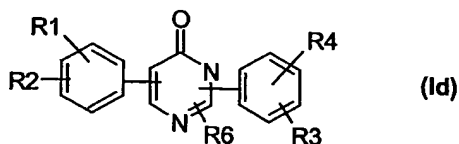
In yet another embodiment of the present invention, there is provided a process for the preparation of novel compounds of the formula (I)



wherein A represents



wherein any of R<sup>7</sup> represents halogen atom and R<sup>6</sup> is as defined earlier may be prepared by converting the compound of formula (Id)

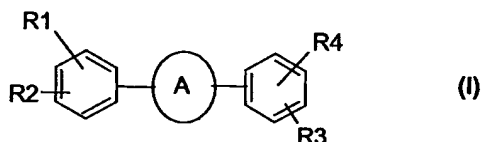


wherein R<sup>6</sup> is as defined earlier.

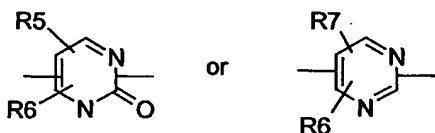
The compound of formula (Id) is prepared according to the procedure described in our PCT application No. PCT/IB03/01289.

The conversion of compound of formula (Id) is carried out using reagents such as phosphorusoxychloride, thionyl chloride, phosphorus trichloride, phosphorus pentachloride, oxalyl chloride and the like in the presence or absence of solvent such as toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, diphenyl ether and the like or a mixture thereof, in presence or absence of dimethylformamide, N,N-dimethylaniline, N,N-diethylaniline and the like. The reaction is carried out at a temperature in the range of 20 °C to reflux temperatures for a period in the range of 2 to 12 h.

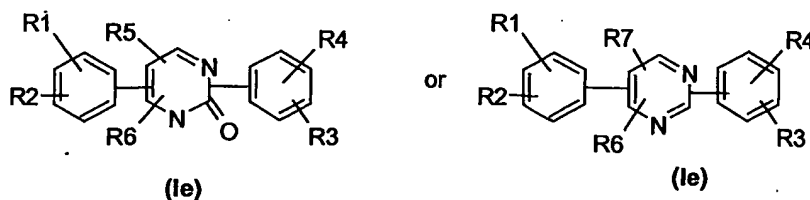
In yet another embodiment of the present invention, there is provided a process for the preparation of novel compounds of the formula (I)



wherein A represents



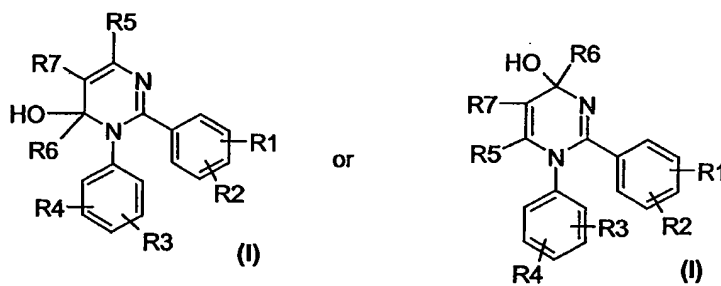
wherein R<sup>6</sup> represents azido, hydrazine or hydrazine derivatives, R<sup>5</sup> and R<sup>7</sup> are as defined above may be prepared by converting the compound of formula (Ie)



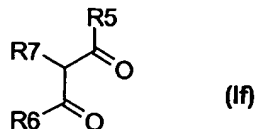
wherein  $R^6$  represents halogen atom and all other symbols are as defined earlier.

The conversion of formula (Ie) may be carried out in the presence of one or more equivalents of metal azide such as  $LiN_3$ ,  $NaN_3$ , trialkyl silylazide and the like or hydrazine hydrate or substituted hydrazine. The reaction may be carried out in the presence of solvent such as toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetone, ethylacetate, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, ethanol, methanol, isopropylalcohol, tert-butylalcohol, diphenyl ether and the like or a mixture thereof. The reaction may be carried out at a temperature in the range of ambient temperature to reflux temperature of the solvent, preferably at a temperature in the range of 80 °C to 100 °C. The reaction time may range from 0.5 to 18 h.

In yet another embodiment of the present invention, there is provided a process for the preparation of novel compounds of the formula (I)

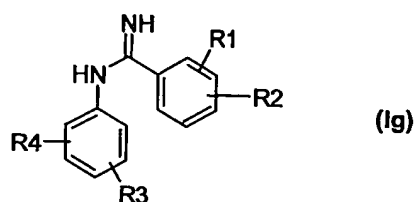


wherein all symbols are as defined earlier may be prepared by a process which comprises reacting a compound of the formula (If)



where all symbols are as defined earlier with a compound of formula (Ig)

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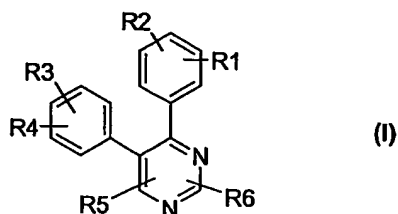


where all symbols are as defined earlier.

The reaction of compound of formula (If) with compound of formula (Ig) may be carried out using appropriate solvents like toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetone, ethylacetate, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, ethanol, methanol, isopropylalcohol, tert-butylalcohol, acetic acid, propionic acid, diphenyl ether etc., a mixture thereof or the like. The condensation reaction is carried out using acidic condition: mineral or organic acids, or basic conditions viz. carbonates, bicarbonates, hydrides, hydroxides, alkyls and alkoxides of alkali metals and alkaline earth metals or by neat reaction. The reaction is carried out using phase transfer catalysts viz. triethylbenzylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium hydrogensulphate, tricaprylmethylammonium chloride (aliquat 336) and the like. The reaction is carried out using polyphosphoric acid, phosphorus pentoxide, sulphuric acid and the like. The reaction is usually carried out under cooling to refluxing conditions. The final product is purified by using chromatographic techniques or by recrystallization.

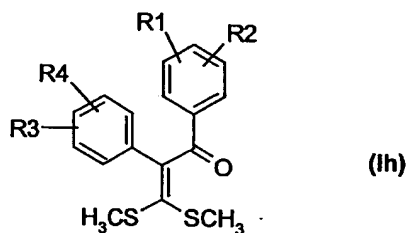
According to yet another embodiment of the present invention, there is provided a process for the preparation of novel compounds of the formula (I)

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wherein all symbols are as defined earlier, which comprises

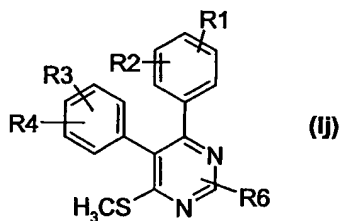
i) reacting a compound of formula (Ih)



where all symbols are as defined earlier with a compound of formula (Ii)



where R<sup>6</sup> is as defined earlier to produce compound of formula (Ij)



and

ii) converting the compound of formula (Ij) to produce compound of formula (I) where all symbols are as defined earlier by reacting with suitable nucleophilic reagent.

The reaction of compound of formula (Ii) with compound of formula (Ij) may be carried out using appropriate solvents like toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-



dichlorobenzene, acetone, ethylacetate, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, ethanol, methanol, isopropylalcohol, tert-butylalcohol, acetic acid, propionic acid, diphenyl ether etc., a mixture thereof or the like. The condensation reaction is carried out using acidic condition: mineral or organic acids, or basic conditions viz. carbonates, bicarbonates, hydrides, hydroxides, alkyls and alkoxides of alkali metals and alkaline earth metals or by neat reaction. The reaction is carried out using phase transfer catalysts viz. triethylbenzylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium hydrogensulphate, tricaprylmethylammonium chloride (aliquat 336) and the like. The reaction is usually carried out under cooling to refluxing conditions. The final product is purified by using chromatographic techniques or by recrystallization.

The conversion of compound of formula (Ij) to compound of formula (I) may be carried out using conventional methods.

In yet another embodiment of the present invention, there is provided a process for the preparation of compounds of formula (I) wherein any of the groups  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$  represent hydrazine derivatives such as acylhydrazide may be prepared by reacting the compound of formula (I) wherein any of the groups  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$  represent hydrazine.

The reaction is carried out using reagents such as acetyl chloride, benzoyl chloride, acetic anhydride, trifluoroacetic anhydride, trichloroacetic anhydride and the like. The reaction may be carried out in the presence of solvent such as toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetonitrile, dimethylsulfoxide, diphenyl ether and the like or a mixture thereof in the presence of base such as carbonates, bicarbonates, hydrides, hydroxides, alkyls and alkoxides of alkali metals and

alkaline earth metals; organic bases such as pyridine, triethyl amine and the like; acids like perchloric acid etc. The reaction may be carried out at a temperature in the range of ambient temperature to reflux temperature of the solvent.

According to yet another embodiment of the present invention there is provided a process for the conversion of novel compounds of the formula (I) wherein the groups  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$  represent alkylthio or arylthio to compounds of formula (I) wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$  represent alkylsulfonyl, alkylsulfinyl, aryl sulfinyl or arylsulfonyl using suitable oxidising reagent. The oxidizing may be selected from potassium peroxymonosulfate (Oxone), hydrogen peroxide, tert-butylperoxide, Jones reagent, peracid [e.g. peracetic acid, perbenzoic acid, m-chloroperbenzoic acid etc], chromic acid, potassium permanganate, alkali metal periodate [e.g. sodium periodate, etc], magnesium mono peroxyphthalate, osmium tetroxide/N-methylmorpholine-N-oxide, sodium tungstate, and the like. The oxidation is usually carried out in a solvent which does not adversely influence the reaction such as acetic acid, dichloromethane, acetone, ethyl acetate, chloroform, water, an alcohol [eg. methanol, ethanol, etc.], a mixture thereof or the like. The reaction is usually carried out under cooling to refluxing conditions.

According to yet another embodiment of the present invention there is provided a process for the conversion of novel compounds of the formula (I) wherein any of the groups  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$  represent alkylsulfonyl may be converted to compounds of the formula (I) wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$  represent sulfamoyl group using the procedure described in the literature (Huang et.al. Tetrahedron Lett. 1994, 39, 7201).

It is appreciated that in any of the above-mentioned reactions, any reactive group in the substrate molecule may be protected according to conventional

chemical practice. Suitable protecting groups in any of the above-mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected.

The pharmaceutically acceptable salts are prepared by reacting the compound of formula (I) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium isopropoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, tetrahydrofuran, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases such as diethanolamine,  $\alpha$ -phenylethylamine, benzylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, guanidine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. Amino acid such as glycine, alanine, cystine, cysteine, lysine, arginine, phenylalanine, etc may be used for the preparation of amino acid salts. Alternatively, acid addition salts wherever applicable are prepared by the treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and in solvents like ethyl acetate, ether, alcohols, acetone, tetrahydrofuran, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include

use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula (I) may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula (I) may be prepared by hydrolysing the pure diastereomeric amide.

Various polymorphs of compound of general formula (I) forming part of this invention may be prepared by crystallization of compound of formula (I) under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

Pharmaceutically acceptable solvates of the compounds of formula (I) forming part of this invention may be prepared by conventional methods such as dissolving the compounds of formula (I) in solvents such as water, methanol, ethanol, mixture of solvents such as acetone:water, dioxane:water, N,N-dimethylformamide:water and the like, preferably water and recrystallizing by using different crystallization techniques.

The novel compounds of the present invention are useful for the treatment of inflammation and immunological diseases. Particularly the compound of the present invention are useful for the treatment of inflammation and immunological diseases those mediated by cytokines such as TNF- $\alpha$ , IL-1, IL-6, IL-1 $\beta$ , IL-8 and cyclooxygenase such as COX-1, COX-2 and COX-3. The compounds of the present invention are also useful for the treatment of rheumatoid arthritis; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; ischemic heart disease; atherosclerosis; cancer; ischemic-induced cell damage; pancreatic  $\beta$  cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever and myalgias due to infection; and the diseases mediated by HIV-1; HIV-2; HIV-3; cytomegalovirus (CMV); influenza; adenovirus; the herpes viruses (including HSV-1, HSV-2) and herpes zoster viruses.

The compounds of the present invention also may possess analgesic properties and may be useful for the treatment of pain disorders, such as hyperalgesia due to excessive IL-1. The compounds of the present invention may also prevent the production of prostaglandins by inhibition of enzymes in the human arachidonic acid/prostaglandin pathway, including cyclooxygenase.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

The present invention provides a pharmaceutical composition, containing the compounds of the general formula (I) as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable hydrates and solvates in combination with the usual pharmaceutically employed carriers, diluents and the like, useful for the treatment of arthritis, pain, fever, psoriasis, allergic diseases, asthma, inflammatory bowel syndrome, gastro-intestinal ulcers, cardiovascular disorders including ischemic heart disease, atherosclerosis, cancer, ischemic-induced cell damage, particularly brain damage caused by stroke, other pathological disorders associated with free radicals. The pharmaceutical composition of the present invention are effective in the treatment of inflammation and immunological diseases, particularly those mediated by cytokines such as TNF- $\alpha$ , IL-1, IL-6, IL-8 and cyclooxygenase such as COX-1, COX-2 and COX-3.

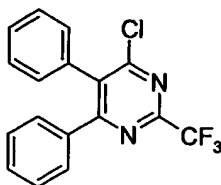
The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, aerosols, suspensions and the like, may contain flavoring agents, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 1 to 20 %, preferably 1 to 10 % by weight of active compound, the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents.

The present invention is provided by the examples given below, which are provided by way of illustration only and should not be considered to limit the scope of the invention.

### **Example 1**

**Synthesis of 4-chloro-5,6-diphenyl-2-(trifluoromethyl)pyrimidine**

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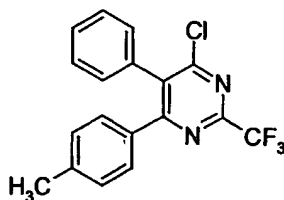


5,6-Diphenyl-2-(trifluoromethyl)pyrimidin-4(3H)-one (8.0g, 25mmol) (synthesized according to the procedure described in our PCT application No. IB03/01289) was refluxed in phosphorus oxychloride (15ml) for 5 hours and allowed to cool to room temperature. The reaction mixture was poured onto ice-water mixture and neutralised with saturated sodium bicarbonate solution. The solid thus separated was extracted with dichloromethane. The organic extract was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to give crude product, which was purified by column chromatography to afford the title compound (6.5g, 76.6%, HPLC purity 99.8%), mp: 105 – 107 °C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.19 – 7.41 (m, 10H). MS m/z: 335.1(M<sup>+</sup>).

### Example 2

Synthesis of 4-chloro-6-(4-methylphenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine



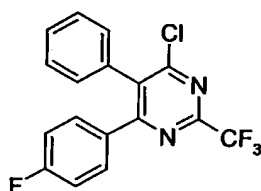
The title compound was prepared from 6-(4-methylphenyl)-5-phenyl-2-(trifluoromethyl)pyrimidin-4(3H)-one (1.4g, 4.2mmol) by following the

procedure described in example 1 (0.68g, 46 %, HPLC purity 99.6%), mp: 97 – 100 °C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  2.30 (s, 3H), 7.03 – 7.05 (d, 2H), 7.22 – 7.30 (m, 4H), 7.41 – 7.42 (m, 3H). MS m/z: 349.2 ( $\text{M}^+$ ).

### **Example 3**

#### **Synthesis of 4-chloro-6-(4-fluorophenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine**

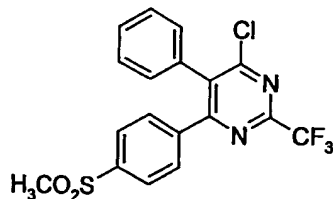


The title compound was prepared from 6-(4-fluorophenyl)-5-phenyl-2-(trifluoromethyl)pyrimidin-4(3H)-one (3.2g, 9.57mmol) by following the procedure described in example 1 (3.3g, 97.7%, HPLC purity 99.5% ), mp: 67 – 68 °C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  6.90 – 6.95 (m, 2H), 7.19 – 7.26 (m, 2H), 7.39 – 7.44 (m, 5H). MS m/z: 353.2 ( $\text{M}^+$ ).

### **Example 4**

#### **Synthesis of 4-chloro-6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidine**



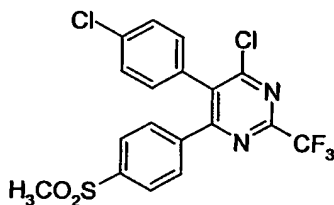


The title compound was prepared from 6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidin-4(3H)-one (3.3g, 8.3mmol) by following the procedure described in example 1 (2.6g, 76%, HPLC purity 98.1% ), mp: 156 – 159°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 3.02 (s, 3H), 7.18 – 7.21(d, 2H), 7.42 – 7.45 (m, 3H), 7.56 – 7.58 (d, 2H), 7.81 – 7.83 (d, 2H). MS m/z: 413.1(M<sup>+</sup>). IR (KBr) cm<sup>-1</sup>: 1138 (-SO<sub>2</sub>-).

### Example 5

**Synthesis of 4-chloro-5-(4-chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine**



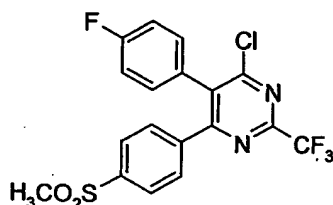
The title compound was prepared from 5-(4-chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidin-4(3H)-one (10.5g, 24.4mmol) by following the procedure described in example 1 (9.3g, 85.32%, HPLC purity 98.92% ), mp: 188 – 190 °C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 3.04 (s, 3H), 7.14 – 7.16 (d, 2H), 7.41 – 7.43 (d, 2H), 7.57 – 7.59 (d, 2H), 7.86 – 7.88 (d, 2H). IR (KBr) cm<sup>-1</sup>: 1135 (-SO<sub>2</sub>-).

### Example 6

**Synthesis of 4-chloro-5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine**

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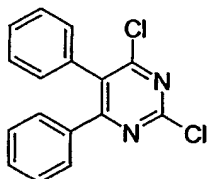


The title compound was prepared from 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidin-4(3H)-one (0.35g, 0.85mmol) by following the procedure described in example 1 (0.25g, 68.4%, HPLC purity 99.6% ), mp: 195 – 197°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 3.04 (s, 3H), 7.11 – 7.21 (m, 4H), 7.56 – 7.58 (d, 2H), 7.85 – 7.87 (d, 2H). MS m/z: 431.2 (M<sup>+</sup>). IR (KBr) cm<sup>-1</sup>: 1136 (-SO<sub>2</sub>-).

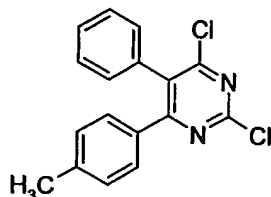
### **Example 7**

#### **Synthesis of 2,4-dichloro-5,6-diphenylpyrimidine**



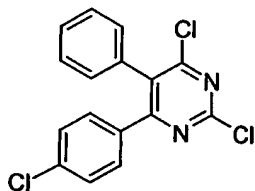
5,6-Diphenyl-uracil (0.21g, 0.8mmol) was refluxed in phosphorus oxychloride (3ml) for 3 hours and allowed to cool to room temperature. The reaction mixture was poured onto ice-water mixture and neutralised with saturated sodium bicarbonate solution. The solid thus separated was extracted with dichloromethane. The organic extract was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the title compound (0.08 g, 34%, HPLC purity 96.9%), mp: 144 – 146°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.16 – 7.39 (m, 10H). MS m/z: 301.1(M<sup>+</sup>).

**Example 8****Synthesis of 2,4-dichloro-6-(4-methylphenyl)-5-phenylpyrimidine**

The title compound was prepared from 6-(4-methylphenyl)-5-phenyl-uracil (0.87g, 3.1mmol) by following the procedure described in example 7 (0.38g, 38.6%, HPLC purity 100%), mp: 130 – 132°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.29 (s, 3H), 7.01 – 7.17 (d, 2H), 7.19 – 7.26 (m, 4H), 7.38 – 7.40 (d, 3H). MS m/z: 316.8 (M<sup>+</sup>).

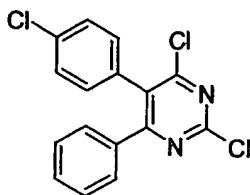
**Example 9****Synthesis of 6-(4-chlorophenyl)-2,4-dichloro-5-phenylpyrimidine**

The title compound was prepared from 6-(4-chlorophenyl)-5-phenyl-uracil (0.4g, 1.33mmol) by following the procedure described in example 7 (0.28g, 62.4%, HPLC purity 98.4%), mp: 129 – 131°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.15 – 7.21 (m, 4H), 7.28 – 7.39 (m, 2H), 7.40 – 7.41 (m, 3H). MS m/z: 336.9 (M<sup>+</sup>).

**Example 10****Synthesis of 5-(4-chlorophenyl)-2,4-dichloro-6-phenylpyrimidine**

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The title compound was prepared from 5-(4-chlorophenyl)-6-phenyl-uracil (0.59g, 2mmol) by following the procedure described in example 7 (0.43g, 65.2%, HPLC purity 100%), mp: 123 – 125°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.10 – 7.13 (d, 2H), 7.24 – 7.36 (m, 7H). MS m/z: 336.9 (M<sup>+</sup>).

#### **Example 11**

##### **Synthesis of 2,4-dichloro-5-(4-methoxyphenyl)-6-phenylpyrimidine**



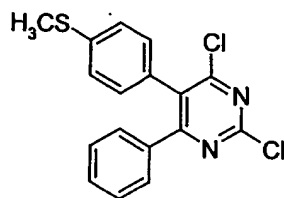
The title compound was prepared from 5-(4-methoxyphenyl)-6-phenyl-uracil (1.5g, 5.1mmol) by following the procedure described in example 7 (1g, 59.2%, HPLC purity 99.4%), mp: 132 – 134°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 3.82 (s, 3H), 6.87 – 6.9 (d, 2H), 7.07– 7.09 (d, 2H), 7.26 – 7.36 (m, 5H). MS m/z: 332.9 (M<sup>+</sup>).

#### **Example 12**

##### **Synthesis of 2,4-dichloro-5-[4-(methylthio)phenyl]-6-phenylpyrimidine**

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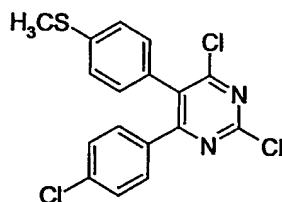


The title compound was prepared from 5-[4-(methylthio)phenyl]-6-phenyl-uracil (0.28g, 2.6mmol) by following the procedure described in example 7 (0.22g, 68.6%, HPLC purity 100%), mp: 88 – 90°C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  2.49 (s, 3H), 7.06 – 7.08 (d, 2H), 7.2 – 7.36 (m, 7H). MS  $m/z$ : 349 ( $\text{M}^+$ ).

### Example 13

Synthesis of 2,4-dichloro-6-(4-chlorophenyl)-5-[4-(methylthio)phenyl]pyrimidine

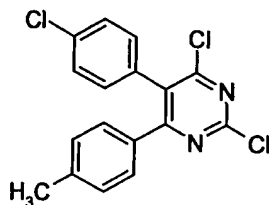


The title compound was prepared from 6-(4-chlorophenyl)-5-[4-(methylthio)phenyl]uracil (0.4g, 1.1mmol) by following the procedure described in example 7 (0.23g, 52%, HPLC purity 99.7%), mp: 144 – 146°C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  2.51 (s, 3H), 7.06 – 7.08 (d, 2H), 7.21 – 7.29 (m, 4H), 7.30 – 7.32 (d, 2H). MS  $m/z$ : 381.9 ( $\text{M}^+$ ).

### Example 14

Synthesis of 2,4-dichloro-5-(4-chlorophenyl)-6-(4-methylphenyl)pyrimidine

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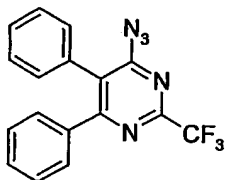


The title compound was prepared from 5-(4-chlorophenyl)-6-(4-methylphenyl)-uracil (0.34g, 1.1mmol) by following the procedure described in example 7 (0.25g, 65.8%, HPLC purity 97.6%), mp: 223 – 225°C.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 2.26 (s, 3H), 7.10 - 7.12 (d, 2H), 7.19 - 7.21 (d, 2H), 7.32 - 7.34 (d, 2H), 7.47 - 7.57 (d, 2H). MS m/z: 350.9 (M<sup>+</sup>).

### Example 15

#### Synthesis of 4-azido-5,6-diphenyl-2-(trifluoromethyl)pyrimidine

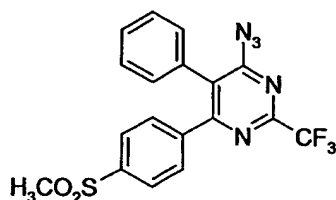


4-Chloro-5,6-diphenyl-2-(trifluoromethyl)pyrimidine (0.5g, 1.5mmol) (synthesized according to the procedure described in example 1) was refluxed in ethanol (10ml) containing sodium azide (0.1g, 1.5mmol) for 8 hours and allowed to cool to room temperature. The reaction mixture was poured onto ice-water mixture. The solid thus separated was extracted with ethyl acetate. The organic extract was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the title compound (0.45g, 88.3%, HPLC purity 98.5%), mp: 126 – 128°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.15 - 7.17 (d, 2H), 7.23 - 7.38 (m, 8H). MS m/z: 342.1(M<sup>+</sup>).

**Example 16**

Synthesis of 4-azido-6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidine

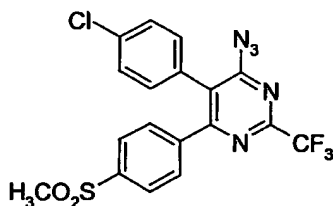


The title compound was prepared from 4-chloro-6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidine (0.5g, 1.2mmol) (synthesized according to the procedure described in example 4) by following the procedure described in example 15 (0.38g, 74.2%, HPLC purity 98%), mp: 172 – 175°C.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 3.21 (s, 3H), 7.27 – 7.3 (d, 2H), 7.38 – 7.39 (d, 3H), 7.54 – 7.56 (d, 2H), 7.84 – 7.86 (d, 2H). MS m/z: 420.1(M<sup>+</sup>). IR (KBr) cm<sup>-1</sup>: 1151 (-SO<sub>2</sub>-).

**Example 17**

Synthesis of 4-azido-5-(4-chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine



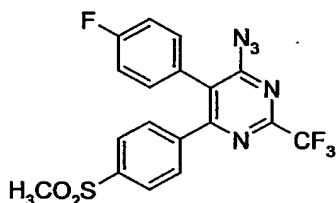
The title compound was prepared from 4-chloro-5-(4-chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine (0.75g, 1.68mmol) (synthesized according to the procedure described in example 5) by following the

procedure described in example 15 (0.6g, 79%, HPLC purity 99%), mp: 317 – 320 °C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  3.03(s, 3H), 7.08 – 7.10 (d, 2H), 7.36 – 7.38 (d, 2H), 7.56 – 7.58 (d, 2H), 7.85 – 7.87 (d, 2H). MS  $m/z$ : 454 ( $\text{M}^+$ ). IR (KBr)  $\text{cm}^{-1}$ : 1148 ( $-\text{SO}_2-$ ).

### Example 18

**Synthesis of 4-azido-5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine**



The title compound was prepared from 4-chloro-5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine (0.75g, 1.74mmol) (synthesized according to the procedure described in example 6) by following the procedure described in example 15 (0.53g, 70%, HPLC purity 99.38%), mp: 285 – 288°C.

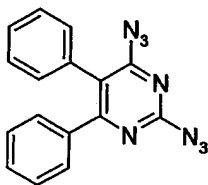
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  3.03(s, 3H), 7.06 – 7.15 (m, 4H), 7.55 – 7.57 (d, 2H), 7.84 – 7.86 (d, 2H). MS  $m/z$ : 438.1( $\text{M}^+$ ). IR (KBr)  $\text{cm}^{-1}$ : 1149 ( $-\text{SO}_2-$ ).

### Example 19

**Synthesis of 2,4-diazido-5,6-diphenylpyrimidine**



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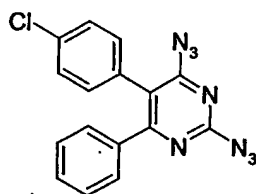


2,4-Dichloro-5,6-diphenylpyrimidine (0.5g, 1.7mmol) (synthesized according to the procedure described for example 7) was refluxed with sodium azide (0.24g, 3.65 mmol) in ethanol (10ml) under stirring for 8 hours. The reaction mixture was poured onto ice-water mixture. The solid thus separated was extracted with ethyl acetate. The organic extract was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to give crude product, which was purified by column chromatography to afford the title compound (0.21g, 40.8%), mp: 132 – 136°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.10 – 7.11(m, 2H), 7.20 – 7.22 (m, 2H), 7.25 – 7.35 (m, 6H). MS m/z: 315.1 (M<sup>+</sup>).

#### **Example 20**

##### **Synthesis of 2,4-diazido-5-(4-chlorophenyl)-6-phenylpyrimidine**

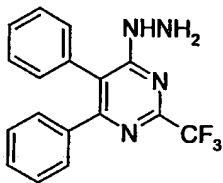


The title compound was prepared from 2,4-dichloro-5-(4-chlorophenyl)-6-phenylpyrimidine (0.3g, 0.89mmol) (obtained according to the procedure described in example 10) by following the procedure described in example 19 (0.15g, 48.2%), mp: 105 – 109°C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.04 – 7.07 (d, 2H), 7.24 – 7.34 (m, 7H). MS  $m/z$ : 349.1 ( $\text{M}^+$ ).

### Example 21

#### Synthesis of 4-hydrazino-5,6-diphenyl-2-(trifluoromethyl)pyrimidine

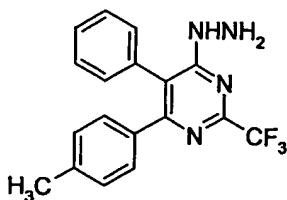


4-Chloro-5,6-diphenyl-2-(trifluoromethyl)pyrimidine (1.8g, 5.3mmol) (synthesized according to the procedure described in example 1) was stirred in ethanol (10 ml) containing hydrazine hydrate (0.64g, 12.8mmol) for 2 hours at 35°C. The crystals thus obtained in the reaction mixture was filtered under vacuum, washed with ethanol (5 ml) and dried to yield the title compound (1.7g, 95.7%, HPLC purity 99.2%), mp: 182 – 186°C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  4.0 (bs, 2H,  $\text{D}_2\text{O}$  exchangeable), 6.20 (s, 1H,  $\text{D}_2\text{O}$  exchangeable), 7.15 – 7.41 (m, 10H). MS  $m/z$ : 331.2 ( $\text{M}^+$ ). IR (KBr)  $\text{cm}^{-1}$ : 3328, 3271, 3029 (-NH-).

### Example 22

#### Synthesis of 4-hydrazino-6-(4-methylphenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine

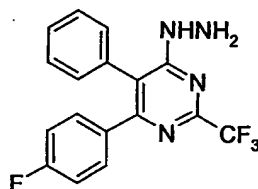


The title compound was prepared from 4-chloro-6-(4-methylphenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine (0.55g, 1.6mmol) (synthesized according to the procedure described in example 2) by following the procedure described in example 21 (0.54g, 99.4%, HPLC purity 99.7%), mp: 188 – 191°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.27 (s, 3H), 4.0 (bs, 1H, D<sub>2</sub>O exchangeable), 6.2 (s, 1H, D<sub>2</sub>O exchangeable), 6.98 – 7.0 (d, 2H), 7.15 – 7.18 (d, 2H), 7.22 – 7.26 (m, 3H), 7.4 – 7.42 (m, 3H). MS m/z: 345.2 (M<sup>+</sup>). IR (KBr) cm<sup>-1</sup>: 3313, 3203, 3046 (-NH-).

### Example 23

Synthesis of 4-hydrazino-6-(4-fluorophenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine

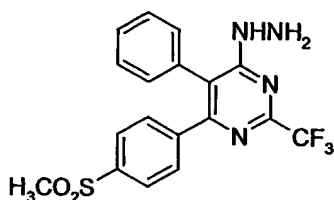


The title compound was prepared from 4-chloro-6-(4-fluorophenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine (2.8g, 7.9mmol) (synthesized according to the procedure described in example 3) by following the procedure described in example 21 (2.3g, 83.3%, HPLC purity 99.4%), mp: 175 – 177 °C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 4.0 (bs, 2H, D<sub>2</sub>O exchangeable), 6.2 (s, 1H, D<sub>2</sub>O exchangeable), 6.85 – 6.90 (m, 2H), 7.14 – 7.16 (m, 2H), 7.32 – 7.43 (m, 5H). MS m/z: 349.2 (M<sup>+</sup>). IR (KBr) cm<sup>-1</sup>: 3327, 3270 (-NH-).

**Example 24**

**Synthesis of 4-hydrazino-6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidine**

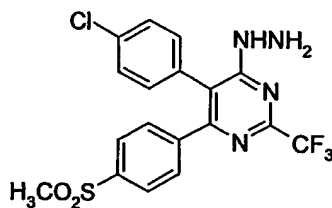


The title compound was prepared from 4-chloro-6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidine (0.41g, 1mmol) (synthesized according to the procedure described in example 4) by following the procedure described in example 21 (0.37g, 91.1%, HPLC purity 97.5%), mp: 272 – 275°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.99 (s, 3H), 4.09 (bs, 2H, D<sub>2</sub>O exchangeable), 6.31 (s, 1H, D<sub>2</sub>O exchangeable), 7.14 – 7.16 (d, 2H), 7.42 – 7.43 (d, 3H), 7.52 – 7.54 (d, 2H), 7.76 – 7.78 (d, 2H). MS m/z: 408.41 (M<sup>+</sup>). IR (KBr) cm<sup>-1</sup>: 3330, 3246 (-NH-), 1149 (-SO<sub>2</sub>-).

**Example 25**

**Synthesis of 5-(4-chlorophenyl)-4-hydrazino-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine**



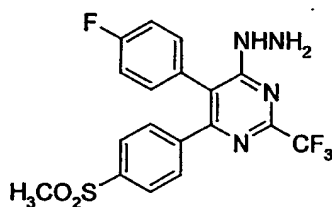
The title compound was prepared from 4-chloro-5-(4-chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine (5.9g, 13.2mmol)

(synthesized according to the procedure described in example 5) by following the procedure described in example 21 (5.11g, 87.5%, HPLC purity 99.51%), mp: 266 – 269 °C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 3.01 (s, 3H), 4.0 (bs, 2H, D<sub>2</sub>O exchangeable), 6.25 (s, 1H, D<sub>2</sub>O exchangeable), 7.09 – 7.11 (d, 2H), 7.42 – 7.44 (d, 2H), 7.50 – 7.53 (d, 2H), 7.80 – 7.82 (d, 2H). MS m/z: 443.1 (M<sup>+</sup>). IR (KBr) cm<sup>-1</sup>: 3333, 3235 (-NH-), 1144(-SO<sub>2</sub>-).

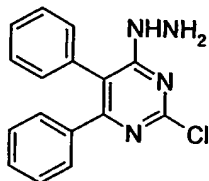
### **Example 26**

**Synthesis of 5-(4-fluorophenyl)-4-hydrazino-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine**



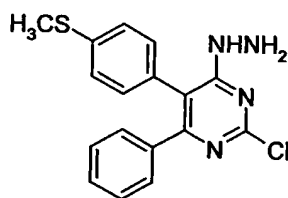
The title compound was prepared from 4-chloro-5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine (0.4g, 0.93mmol) (synthesized according to the procedure described in example 6) by following the procedure described in example 21 (0.25g, 63%, HPLC purity 97.7%), mp: 286 – 290°C.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 3.18 (s, 3H), 4.54 (bs, 2H, D<sub>2</sub>O exchangeable), 7.21 – 7.25 (m, 4H), 7.45 – 7.47 (d, 2H), 7.78 – 7.80 (d, 2H), 8.2 (s, 1H, D<sub>2</sub>O exchangeable). MS m/z: 427.1 (M<sup>+</sup>). IR (KBr) cm<sup>-1</sup>: 3327, 3242 (-NH-), 1149 (-SO<sub>2</sub>-).

**Example 27****Synthesis of 2-chloro-5,6-diphenyl-4-hydrazinopyrimidine**

2,4-Dichloro-5,6-diphenylpyrimidine (2.0g, 6.6mmol) (synthesized according to the procedure described in example 7) was treated with hydrazine hydrate (0.73g, 14.6mmol) in ethanol (10ml) under stirring for 5 hours at room temperature. The reaction mixture was poured onto ice-water mixture. The solid thus separated was extracted with diethylether. The organic extract was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the title compound (0.64g, 32.5%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  4.0 (bs, 2H,  $\text{D}_2\text{O}$  exchangeable), 6.2 (s, 1H,  $\text{D}_2\text{O}$  exchangeable), 7.12 – 7.38 (m, 10H). MS  $m/z$ : 297.3 ( $\text{M}^+$ ).

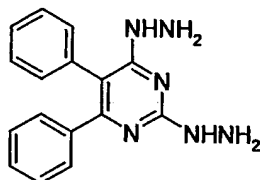
**Example 28****Synthesis of 2-chloro-4-hydrazino-5-[4-(methylthio)phenyl]-6-phenylpyrimidine**

The title compound was prepared from 2,4-dichloro-5-[4-(methylthio)phenyl]-6-phenylpyrimidine (1.0g, 2.9mmol) (obtained according to the procedure described in example 12) by following the procedure described in example 27 (0.33g, 33.4%, HPLC purity 98.6%), mp: 272 – 274 °C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  2.48 (s, 3H), 3.99 (bs, 2H,  $\text{D}_2\text{O}$  exchangeable), 6.15 (s, 1H,  $\text{D}_2\text{O}$  exchangeable), 7.02 – 7.04 (d, 2H), 7.19 – 7.31 (m, 7H). MS  $m/z$ : 343.1 ( $\text{M}^+$ ). IR (KBr)  $\text{cm}^{-1}$ : 3272 ( $-\text{NH}-$ ).

### Example 29

#### Synthesis of 2,4-dihydrazino-5,6-diphenylpyrimidine

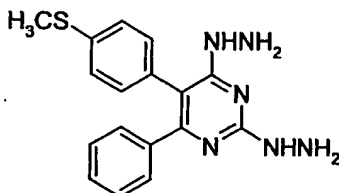


2,4-Dichloro-5,6-diphenylpyrimidine (0.5g, 1.7mmol) (synthesized according to the procedure described in example 7) was refluxed with hydrazine hydrate (0.18g, 3.6mmol) in ethanol (10ml) under stirring for 6 hours. The reaction mixture was poured onto ice-water mixture. The solid thus separated was extracted with dichloromethane. The organic extract was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the title compound (0.12g, 25%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  3.96 (bs, 3H,  $\text{D}_2\text{O}$  exchangeable), 5.93 (s, 1H,  $\text{D}_2\text{O}$  exchangeable), 6.34 (s, 1H,  $\text{D}_2\text{O}$  exchangeable), 7.08 – 7.18 (m, 5H), 7.28 – 7.32 (m, 5H). MS  $m/z$ : 293.2 ( $\text{M}^+$ ).

### Example 30

#### Synthesis of 2,4-dihydrazino-5-[4-(methylthio)phenyl]-6-phenylpyrimidine

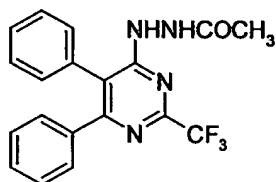


The title compound was prepared from 2,4-dichloro-5-[4-(methylthio)phenyl]-6-phenylpyrimidine (0.32g, 0.93mmol) (synthesized according to the procedure described in example 12) by following the procedure described in example 29 (0.26g, 81.2%, HPLC purity 95.8%), mp: 207 – 210 °C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.46 (s, 3H), 4.0 (bs, 4H, D<sub>2</sub>O exchangeable), 5.91 (s, 1H, D<sub>2</sub>O exchangeable), 6.35 (s, 1H, D<sub>2</sub>O exchangeable), 7.0 – 7.02 (d, 2H), 7.16 – 7.31 (m, 7H). MS m/z: 339.2 (M<sup>+</sup>). IR (KBr) cm<sup>-1</sup>: 3308, 3257 (-NH-).

### Example 31

**Synthesis of N'-[5,6-diphenyl-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide**



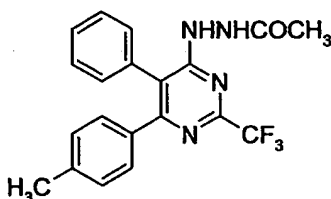
4-Hydrazino-5,6-diphenyl-2-(trifluoromethyl)pyrimidine (0.7g, 2.1mmol) (synthesized according to the procedure described in example 21) in pyridine (10 ml) was added acetylchloride (0.17g, 2.2mmol) dropwise at 20 °C under stirring for 10 minutes. After 30 minutes of stirring, the reaction mixture was poured onto ice-water mixture, acidified to pH 4 using hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography to furnish the title compound (0.2g, 25.4%, HPLC purity 99.4%), mp: 113 – 116°C.



$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  2.12 (s, 3H), 7.19 – 7.22 (m, 3H, 1H is  $\text{D}_2\text{O}$  exchangeable), 7.26 – 7.45 (m, 8H), 8.0 – 8.2 (s, 1H,  $\text{D}_2\text{O}$  exchangeable). MS  $m/z$ : 373.2 ( $\text{M}^+$ ). IR (KBr)  $\text{cm}^{-1}$ : 3330, 3268 (–NH–), 1686 (–C=O).

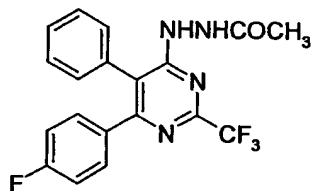
### Example 32

#### Synthesis of N'-[6-(4-methylphenyl)-5-phenyl-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide



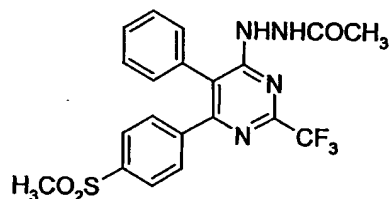
To a solution of 4-hydrazino-6-(4-methylphenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine (0.23g, 0.66mmol) (synthesized according to the procedure described in example 22) in dichloromethane (5 ml) and pyridine (0.06g, 0.8mmol), acetyl chloride (0.6g, 0.7mmol) was added dropwise at room temperature over a period of ten minutes under stirring. Stirring was continued for two hours and the resultant reaction mass was poured onto ice-water mixture and neutralised with hydrochloric acid. The reaction mixture was extracted with dichloromethane. The organic extract was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the title compound (0.2g, 77.9%, HPLC purity 99.4%), mp: 147 – 152°C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  2.11 (s, 3H), 2.27 (s, 3H), 6.99 – 7.01 (d, 2H), 7.22 – 7.28 (m, 5H, 1H is  $\text{D}_2\text{O}$  exchangeable), 7.42 – 7.44 (m, 3H), 8.0 (d, 1H,  $\text{D}_2\text{O}$  exchangeable). MS  $m/z$ : 387.2 ( $\text{M}^+$ ). IR (KBr)  $\text{cm}^{-1}$ : 3287(–NH–), 1670 (–C=O).

**Example 33****Synthesis of N'-[6-(4-fluorophenyl)-5-phenyl-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide**

The title compound was prepared from 4-hydrazino-6-(4-fluorophenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine (0.8g, 2.3mmol) (synthesized according to the procedure described in example 23) by following the procedure described in example 32 (0.84g, 93.5%, HPLC purity 97.9%), mp: 149 – 153 °C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.1 (s, 3H), 6.87 – 6.91 (m, 2H), 7.26 – 7.27 (m, 1H, D<sub>2</sub>O exchangeable), 7.32 – 7.46 (m, 7H), 8.0 (d, 1H, D<sub>2</sub>O exchangeable). MS m/z: 391.1 (M<sup>+</sup>). IR (KBr) cm<sup>-1</sup>: 3376, 3261 (-NH-), 1669 (-C=O).

**Example 34****Synthesis of N'-[6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide**

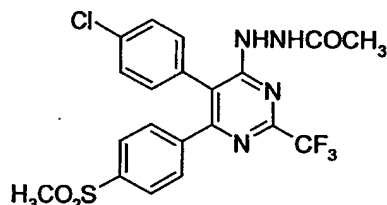
The title compound was prepared from 4-hydrazino-6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidine (0.45g, 1.1mmol) (synthesized according to the procedure described in example in 24) by

following the procedure described in example 32 (0.29g, 58.5%, HPLC purity 99.6%), mp: 265 – 268 °C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.9 (s, 3H), 3.18 (s, 3H), 7.24 – 7.26 (d, 2H), 7.39 – 7.48 (m, 5H), 7.76 – 7.86 (d, 2H), 8.7 (s, 1H,  $\text{D}_2\text{O}$  exchangeable), 10 (s, 1H,  $\text{D}_2\text{O}$  exchangeable). MS  $m/z$ : 451.2 ( $\text{M}^+$ ). IR (KBr)  $\text{cm}^{-1}$ : 3331 (-NH-), 1693 (-C=O), 1148(- $\text{SO}_2$ -).

### Example 35

Synthesis of N'-[5-(4-chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide

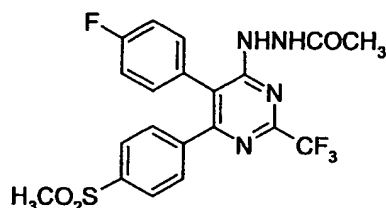


The title compound was prepared from 5-(4-chlorophenyl)-4-hydrazino-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine (1.0g, 2.2mmol) (synthesized according to the procedure described in example 25) by following the procedure described in example 32 (0.8g, 73.2%, HPLC purity 99.8%), mp: 254 – 256 °C.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ):  $\delta$  1.9 (s, 3H), 3.2 (s, 3H), 7.27 – 7.29 (m, 2H), 7.46 – 7.51 (m, 4H), 7.81 – 7.83 (d, 2H), 8.75 (s, 1H,  $\text{D}_2\text{O}$  exchangeable), 10 (s, 1H,  $\text{D}_2\text{O}$  exchangeable). MS  $m/z$ : 485.2 ( $\text{M}^+$ ). IR (KBr)  $\text{cm}^{-1}$ : 3317 (-NH-), 1695 (-C=O), 1152 (- $\text{SO}_2$ -).

**Example 36**

**Synthesis of N'-[5-(6-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide**

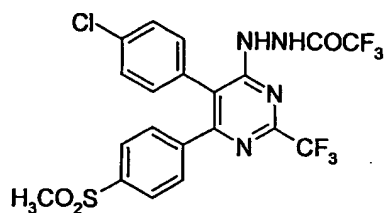


The title compound was prepared from 5-(4-fluorophenyl)-4-hydrazino-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine (0.75g, 1.7mmol) (synthesized according to the procedure described in example 26) by following the procedure described in example 32 (0.7g, 83.7%, HPLC purity 98.4%), mp: 281 – 283 °C.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 1.9 (s, 3H), 3.2 (s, 3H), 7.24 – 7.30 (m, 2H), 7.48 – 7.50 (m, 4H), 7.80 – 7.82 (d, 2H), 8.75 (s, 1H, D<sub>2</sub>O exchangeable), 10 (s, 1H, D<sub>2</sub>O exchangeable). MS m/z: 469.1 (M<sup>+</sup>). IR (KBr) cm<sup>-1</sup>: 3381, 3325 (-NH-), 1694 (-C=O), 1146 (-SO<sub>2</sub>).

**Example 37**

**Synthesis of N'-[5-(4-chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidin-4-yl]trifluoroacetohydrazide**



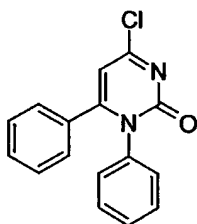
To a solution of 5-(4-chlorophenyl)-4-hydrazino-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine (0.5g, 1.1mmol) (synthesized according to the

procedure described in example 25) in dichloromethane (5 ml) and pyridine (0.1g, 1.2mmol), trifluoroacetic anhydride (0.24g, 1.2mmol) was added dropwise at 0 °C to 10 °C over a period of ten minutes under stirring. Stirring was continued for 0.5 hr and the resultant reaction mass was poured onto ice-water mixture and extracted with dichloromethane. The organic extract was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the title compound (0.3g, 49.3%, HPLC purity 97.6%), mp: 307 – 309 °C.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 3.21 (s, 3H), 7.32 – 7.34 (d, 2H), 7.5 – 7.55 (m, 4H), 7.83 – 7.85 (d, 2H), 9.3 (s, 1H, D<sub>2</sub>O exchangeable), 11.75 (s, 1H, D<sub>2</sub>O exchangeable). MS m/z: 539.2 (M<sup>+</sup>). IR (KBr) cm<sup>-1</sup>: 3404, 3255 (-NH-), 1762 (-C=O), 1153 (-SO<sub>2</sub>).

### **Example 38**

#### **Synthesis of 4-chloro-1,6-diphenylpyrimidine-2(1H)-one**



Oxalyl chloride (3.1g, 24.4mmol) was added to a mixture of N,N-dimethylformamide (1.8g, 24.6mmol) in dichloromethane (30ml) at -5 °C to 0 °C under stirring. After the completion of addition the reaction temperature was allowed to reach 20 °C to 25 °C. 1,6-Diphenyluracil (4.0g, 15.2 mmol) was added in portions to the resulted suspension for 2.5 hrs. The reaction mixture was heated to reflux for 4 hours under stirring and continued stirring for 12 hours at room temperature. The reaction mass was poured onto sodium hydroxide solution

(150ml, 0.25 N) and collected the dichloromethane layer. The dichloromethane layer was washed with hydrochloric acid (200ml, 0.025N), water and saturated sodium chloride solution successively. The organic extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the title compound (1.5g, 35%, HPLC purity 99.8%), mp: 141 – 143 °C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.09 – 7.11 (m, 1H), 7.19 (s, 1H), 7.36 – 7.40 (m, 2H), 7.50 – 7.53 (m, 3H), 7.68 – 7.7 (d, 2H), 8.03 – 8.06 (d, 2H). MS m/z: 283.9 (M<sup>+</sup>). IR (KBr) cm<sup>-1</sup>: 1596 (-C=O).

Described below are the examples of pharmacological assays used for finding out the efficacy of the compounds of the present invention wherein their protocols and results are provided.

#### **Rat Carrageenan Paw Edema Test**

The carrageenan paw edema test was performed as described by Winter et al (Proc.Soc.Exp.Biol.Me., 111, 544, 1962). Male Wistar rats were selected and the body weight were equivalent within each group. The rats were fasted for eighteen hours with free access to water. The rats were dosed orally with the test compound suspended in vehicle containing 0.5% methylcellulose. The control rats were administered the vehicle alone. After one hour the rats were injected with 0.1 ml of 1% Carrageenan solution in 0.9% saline into the sub plantar surface of the right hind paw. Paw thickness was measured using vernier calipers at 0 time, after 2 and 3 hours. The average of foot swelling in drug treated animals was compared with that of control animals. Anti-inflammatory activity was expressed as the percentage inhibition of edema compared with control group [Arzneim-Forsch/Drug Res., 43(I), 1, 44-50,1993; Otterness and Bliven, Laboratory Models for Testing NSAIDs, In Non-Steroidal Anti-Inflammatory Drugs, (J. Lombardino, ed.1985)]. The data of the selected compounds in this

invention are summarized in Table I. In order to evaluate their role on the ulcer formation, the animals were sacrificed by cervical dislocation, the stomach removed and flushed with 1% formalin (10ml). The stomach was opened along the greater curvature. The haemorrhagic puncta and sulci were identified macroscopically. The presence or absence of stomach lesions was scored. The incidence of ulceration was calculated from the number of rats that showed atleast one gastric ulcer or haemorrhagic erosion.

**Table I**

<b>Example No.</b>	<b>Rat Paw Edema model % Inhibition (10mg/kg body weight)</b>
6	64
7	60.9
9	42.8
13	47.8
20	39.4

**In vitro evaluation of Cyclooxygenase-2 (COX-2) inhibition activity**

The compounds of this invention exhibited *in vitro* inhibition of COX-2. The COX-2 inhibition activity of the compounds illustrated in the examples was determined by the following method.

**Human Whole Blood Assay**

Human whole blood provides a protein and cell rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as selective COX-2 inhibitors. Studies have shown that normal human blood does

not contain COX-2 enzyme. This is correlating with the observation that COX-2 inhibitors have no effect on prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) production in normal blood. These inhibitors are active only after incubation of human blood with lipopolysaccharide (LPS), which induces COX-2 production in the blood.

### **Method**

Fresh blood was collected in tubes containing potassium EDTA by vein puncture from male volunteers. The subjects should have no apparent inflammatory conditions and not taken NSAIDs for atleast 7 days prior to blood collection. Blood was treated with aspirin *in vitro* (10µg/ml, at time zero) to inactivate COX-1, and then with LPS (10µg/ml) along with test agents or vehicle. The blood was incubated for 24 h at 37 °C, after which the tubes were centrifuged, the plasma was separated and stored at -80 °C (J.Pharmacol.Exp.Ther., 271, 1705, 1994; Proc.Natl.Acad.Sci. USA., 96, 7563, 1999). The plasma was assayed for PGE<sub>2</sub> using Cayman ELISA kit as per the procedure outlined by the manufacturer (Cayman Chemicals, Ann Arbor, USA). The plasma was also tested for TNF-α, IL-1β, and IL-6 using appropriate human ELISA kit as per the procedure of manufacturer (Cayman Chemicals, Ann Arbor, USA). Representative results of COX-2 inhibition are shown in Table II.

**Table II**

<b>Example No.</b>	<b>Conc. (µM)</b>	<b>COX-2 Inhibition (%)</b>
6	0.1	51.94
9	0.1	60.47
13	0.1	45.67



**Tumor Necrosis Factor Alpha (TNF- $\alpha$ )**

This assay determines the effect of test compounds on the production of TNF- $\alpha$  from human monocytes. Compounds were tested for their ability to downregulate the production of TNF- $\alpha$  in activated monocytes. Test compounds were incubated for three, six and twenty four hours with human monocytes. Lipopolysaccharide was used to stimulate the monocytes. The level of TNF- $\alpha$  was quantitated using Enzyme-Linked Immunosorbent assay performed in a 96 well format. Representative results of TNF- $\alpha$  inhibition are shown in Table III.

**Table III**

Example No.	Conc. ( $\mu$ M)	TNF- $\alpha$ Inhibition (%)
4	10	55.41
6	1	51.48
11	1	29.2
19	10	69.43
20	1	26.34

**Interleukin-6(IL-6)**

This assay determines the effect of test compounds on the production of IL-6 from human monocytes. Compounds are tested for their ability to downregulate the production of IL-6 in activated monocytes. Test compounds were incubated for three, six and twenty four hours with human monocytes. Lipopolysaccharide was used to stimulate the monocytes. The level of Interleukin-6 is quantitated using Enzyme-Linked Immunosorbent assay

performed in a 96 well format. Representative results of IL-6 inhibition are shown in Table IV.

**Table IV**

<b>Example No.</b>	<b>Conc. (<math>\mu</math>M)</b>	<b>IL-6 Inhibition (%)</b>
1	1	62.52
2	1	62.34
21	1	67.47
22	1	52.28
24	10	66.01
32	10	53.33

**Inhibitory Action on Adjuvant Arthritis**

Compounds were assayed for their activity on rat adjuvant induced arthritis according to Theisen-Popp et al., (Agents Actions, 42, 50-55, 1994). Six to seven weeks old, Wistar rats were weighed, marked and assigned to groups [a negative control group in which arthritis was not induced (non-adjuvant control), a vehicle-treated arthritis control group, test substance treated arthritis group]. Adjuvant induced arthritis was induced by an injection of *Mycobacterium butyricum* (Difco) suspended in liquid paraffin into the sub-plantar region of the right hind paw (J.Pharmacol.Exp.Ther., 284, 714, 1998). Body weight, contra-lateral paw volumes were determined at various days (0, 4, 14, 21) for all the groups. The test compound or vehicle was administered orally beginning post injection of adjuvant and continued for 21 days. On day 21, body weight and paw volume of both right and left hind paw, spleen, and thymus weights were determined. In addition, the radiograph of both hind paws was taken to assess the

tibio-tarsal joint integrity. Hind limb below the stifle joint was removed and fixed in 1% formalin saline. At the end of the experiment, plasma samples were analysed for cytokines, interleukins and prostaglandins. The presence or absence of lesions in the stomachs was also observed.

Two-factor ('treatment' and 'time') Analysis of Variance with repeated measures on 'time' were applied to the % changes for body weight and foot volumes. A post hoc Dunnett's test was conducted to compare the effect of treatments to vehicle. A one-way Analysis of Variance was applied to the thymus and spleen weights followed by the Dunnett's test to compare the effect of treatments to vehicle. Dose-response curves for % inhibition in foot volumes on days 4, 14 and 21 were fitted by a 4-parameter logistic function using a nonlinear Least Squares' regression.  $ID_{50}$  was defined as the dose corresponding to a 50% reduction from the vehicle and was derived by interpolation from the fitted 4-parameter equation.

### **DTP Human Tumor Cell Line Screen**

#### **Methodology Of The *In Vitro* Cancer Screen**

The three cell line, one-dose prescreen carried out which identifies a large proportion of the compounds that would be inactive in multi-dose 60 cell line screening. The current assay utilizes a 384 well plate format and fluorescent staining technologies resulting in greater screening capacity for testing of synthetic samples.

#### **Cell Lines**

The cell lines of the cancer screening panel are grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. For a typical screening experiment, cells are inoculated into 96 well microtiter plates in 100

μL. After cell inoculation, the microtiter plates are incubated at 37° C, 5 % CO<sub>2</sub>, 95 % air and 100 % relative humidity for 24 h prior to addition of experimental drugs. The cells are plated a densities of 5000 cells/well (MCF7), 1000 cells/well (NCI-H460), and 7500 cells/well (SF-268) to allow for varying doubling time of the cell lines. Each plate contains all three cell lines, a series of dilutions of standard agents, total kill wells and appropriate controls. Plates are incubated under standard conditions for 24 hours prior to addition of experimental compounds or extracts.

#### **Addition of Experimental Agents (Pure Compounds)**

Experimental compounds are solubilized in dimethyl sulfoxide (DMSO) at 400-times the desired maximum test concentration (maximum final DMSO concentration of 0.25%) and stored frozen. Compounds are then diluted with complete media with 0.1% gentamicin sulfate (5 μl of test sample in 100% DMSO is added to 565 μl of complete medium). 20 μl of this solution is then dispensed into test wells containing 50 μl of cell suspension to yield a test concentration of 1.00E-04M.

Two standard drugs, meaning that their activities against the cell lines are well documented, are tested against each cell line: NSC 19893 (5-FU) and NSC 123127 (Adriamycin).

#### **Endpoint Measurement**

After compound addition, plates are incubated at standard conditions for 48 hours, 10 μl/well Alamar Blue is added and the plates are incubated for an additional 4 hours. Fluorescence is measured using an excitation wavelength of 530 nm and an emission wavelength of 590 nm.

Calculation of Percent Test Cell Growth/Control (untreated) Cell Growth (T/C)

**Calculation of Percent Test Cell Growth/Control (untreated) Cell Growth (T/C)**

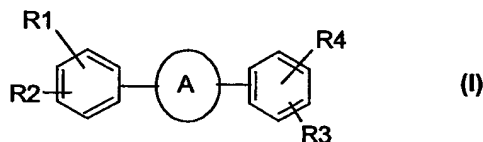
Percent growth is calculated on a plate-by-plate basis for test wells relative to control wells. Percent Growth is expressed as the ratio of fluorescence of the test well to the average fluorescence of the control wells x 100. The results are shown in table V.

**Table V**

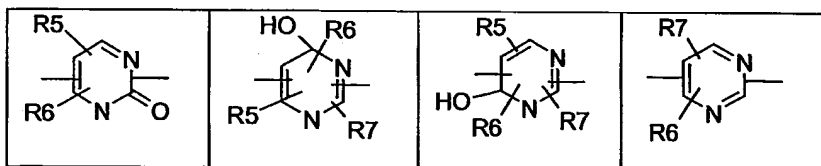
Example No.	Concentration (100 $\mu$ m)		
	Percentage Growth		
	Lung	Breast	CNS
	NCI-H460	MCF7	SF-268
4	0	0	3
6	0	0	12
8	1	5	6
9	0	1	1
10	0	0	0
11	0	5	2
12	0	-1	4

## Claims :

1. Novel pyrimidine derivatives of the formula (I)



their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  may be same or different and independently represent hydrogen, hydroxy, nitro, nitroso, formyl, azido, halo or substituted or unsubstituted groups selected from alkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; A represents pyrimidine derivative of the formula



wherein  $R_5$ ,  $R_6$ ,  $R_7$ , may be same or different and represent, hydrogen, nitro, nitroso, formyl, azido, halo, or substituted or unsubstituted groups selected from alkyl, alkoxy, acyl, cycloalkyl, haloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; the pyrimidine group may be attached to the phenyl through carbon or nitrogen atom.

2. Novel pyrimidine derivatives as claimed in claim 1, selected from:

4-Chloro-5,6-diphenyl-2-(trifluoromethyl)pyrimidine ;  
4-Chloro-6-(4-methylphenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine ;  
4-Chloro-6-(4-fluorophenyl)-5-phenyl-2-(trifluoromethyl) pyrimidine ;  
4-Chloro-6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidine ;  
4-Chloro-5-(4-chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine ;  
4-Chloro-5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine ;  
2,4-Dichloro-5,6-diphenylpyrimidine ;  
2,4-Dichloro-6-(4-methylphenyl)-5-phenylpyrimidine ;  
6-(4-Chlorophenyl)-2,4-dichloro-5-phenylpyrimidine ;  
5-(4-Chlorophenyl)-2,4-dichloro-6-phenylpyrimidine ;  
2,4-Dichloro-5-(4-methoxyphenyl)-6-phenylpyrimidine ;  
2,4-Dichloro-5-[4-(methylthio)phenyl]-6-phenylpyrimidine ;  
2,4-Dichloro-6-(4-chlorophenyl)-5-[4-(methylthio)phenyl] pyrimidine ;  
2,4-Dichloro-5-(4-chlorophenyl)-6-(4-methylphenyl)pyrimidine ;  
4-Azido-5,6-diphenyl-2-(trifluoromethyl)pyrimidine ;  
4-Azido-6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidine ;  
4-Azido-5-(4-chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine ;  
4-Azido-5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine ;  
2,4-Diazido-5,6-diphenylpyrimidine ;  
2,4-Diazido-5-(4-chlorophenyl)-6-phenylpyrimidine ;  
4-Hydrazino-5,6-diphenyl-2-(trifluoromethyl)pyrimidine ;  
4-Hydrazino-6-(4-methylphenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine ;  
4-Hydrazino-6-(4-fluorophenyl)-5-phenyl-2-(trifluoromethyl)pyrimidine ;

4-Hydrazino-6-[4-(methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidine ;  
5-(4-Chlorophenyl)-4-hydrazino-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine ;  
5-(4-F)-4-hydrazino-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidine ;  
2-Chloro-5,6-diphenyl-4-hydrazinopyrimidine ;  
2-Chloro-4-hydrazino-5-[4-(methylthio)phenyl]-6-phenylpyrimidine ;  
2,4-Dihydrazino-5,6-diphenylpyrimidine ;  
2,4-Dihydrazino-5-[4-(methylthio)phenyl]-6-phenylpyrimidine ;  
N-[5,6-Diphenyl-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide ;  
N-[6-(4-Methylphenyl)-5-phenyl-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide ;  
N-[6-(4-Fluorophenyl)-5-phenyl-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide ;  
N'-[6-[4-(Methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide ;  
N-[5-(4-Chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide ;  
N-[5-(6-Fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidin-4-yl]acetohydrazide ;  
N-[5-(4-Chlorophenyl)-[6-(4-methylsulfonyl)phenyl]-2-(trifluoromethyl)pyrimidin-4-yl]trifluoroacetohydrazide ;  
4-Chloro-1,6-diphenylpyrimidine-2(1H)-one ;  
4-Azido-6-[(4-methylthio)phenyl]-1-phenylpyrimidin-2(1H)-one ;  
4-[3-(4-Chlorophenyl)-2-oxo-6-trifluoromethyl-2,3-dihydro-pyrimidin-4-yl]benzenesulfonamide ;

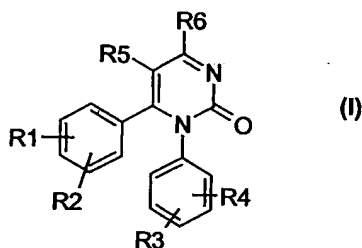


6-(4-Methylsulfonylphenyl)-1-p-tolyl-4-(trifluoromethyl)pyrimidin-2(1H)-one;  
4-Azido-6-(4-methylsulfonylphenyl)-1-p-tolyl-pyrimidin-2(1H)-one;  
4-(6-Azido-3-methoxyphenyl-2-oxo-2,3-dihydropyrimidin-4-yl)benzenesulfonamide;  
4-(6-Azido-4-methoxyphenyl-2-oxo-2,3-dihydropyrimidin-4-yl)benzenesulfonamide;  
2-Chloro-5-(4-chlorophenyl)-4-methylthio-6-[(4-methylthio)phenyl]pyrimidine;  
6-[(4-Methylthio)phenyl]-1-phenyl-4-(trifluoromethyl)pyrimidin-2(1H)-one;  
4-(2-Oxo-3-phenyl-6-trifluoromethyl-2,3-dihydropyrimidin-4-yl)benzenesulfonamide;  
4-Methylthio-5,6-bis(p-tolyl)pyrimidine;  
4-Methylthio-5,6-diphenyl-pyrimidin-2-ol;  
4-Methylsulfonyl-5,6-bis(p-tolyl)pyrimidine;  
1,6-Diphenyl-4-(trifluoromethyl)pyrimidin-2(1H)-one;  
4-(2-Hydroxy-6-methylthio-5-phenylpyrimidin-4-yl)benzenesulfonamide;  
4-Methylthio-6-[(4-methylthio)phenyl]-5-phenylpyrimidine;  
2-Chloro-4-methylthio-5,6-bis(p-tolyl)pyrimidine;  
2-Chloro-4-methylthio-6-[(4-methylthio)phenyl]-5-p-tolyl-pyrimidine;  
5-(4-Bromophenyl)-2-chloro-4-methylthio-6-[(4-methylthio)phenyl]pyrimidine;  
5-(2-Bromophenyl)-4-methylthio-6-[(4-methylthio)phenyl]pyrimidin-2-ol;  
4-(2-Chloro-6-methylthio-5-phenylpyrimidin-4-yl)benzenesulfonamide;  
2-Chloro-4,5-bis-(4-methoxyphenyl)-6-(methylthio)pyrimidine;  
2-Chloro-4-methylthio-6-[(4-methylthio)phenyl]-5-phenylpyrimidine;  
2,4-Diazido-6[(4-methylthio)phenyl]-5-phenylpyrimidine;  
2,4-Diazido-5-(4-bromophenyl)-6-(4-methylthiophenyl)pyrimidine;  
4-Chloro-6-[(4-methylsulfonyl)phenyl]-1-phenylpyrimidin-2(1H)-one;  
4-Azido-1-(2-fluorophenyl)-6-[(4-methylthio)phenyl]-pyrimidin-2(1H)-one;

2-[(4-Methylsulfonyl)phenyl]-6-trifluoromethyl-3-[(4-trifluoromethyl)phenyl]-3,4-dihydropyrimidin-4-ol;

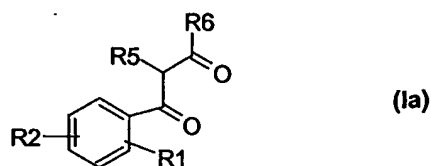
5-(3-Fluorophenyl)-4-methylthio-6-[(4-methylthio)phenyl]pyrimidin-2-ol and 4-(6-Hydroxy-6-methyl-2-p-tolyl-4-trifluoromethyl-6H-pyrimidin-1-yl)benzenesulfonamide.

3. A process for the preparation of novel pyrimidine derivatives of the formula (I)

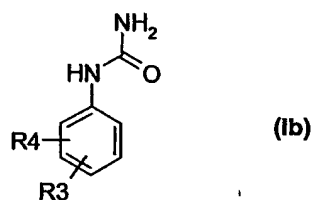


their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  may be same or different and independently represent hydrogen, hydroxy, nitro, nitroso, formyl, azido, halo or substituted or unsubstituted groups selected from alkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives;  $R_5$ ,  $R_6$ , may be same or different and represent, hydrogen, nitro, nitroso, formyl, azido, halo, or substituted or unsubstituted groups selected from alkyl, alkoxy, acyl, cycloalkyl, haloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl,

alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; which comprises condensing a compound of formula (Ia)

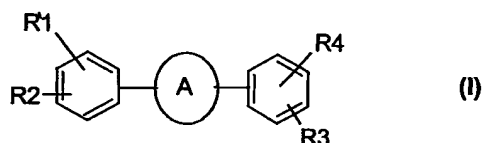


wherein all symbols are as defined above with a compound of the formula (Ib)



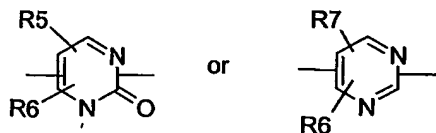
where all symbols are as defined above.

4. A process for the preparation of novel pyrimidine derivatives of the formula (I)

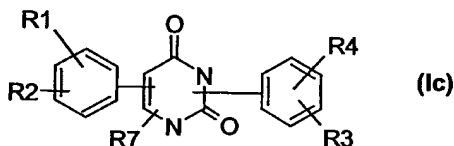


their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> may be same or different and independently represent hydrogen, hydroxy, nitro, nitroso, formyl, azido, halo or substituted or unsubstituted groups selected from alkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio,

arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; A represents pyrimidine derivative of the formula

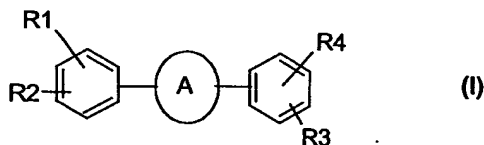


wherein  $R^6$  represents halogen atom,  $R_5$ ,  $R_7$ , may be same or different and represent, hydrogen, nitro, nitroso, formyl, azido, halo, or substituted or unsubstituted groups selected from alkyl, alkoxy, acyl, cycloalkyl, haloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsufonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; the pyrimidine group may be attached to the phenyl through carbon or nitrogen atom; comprising converting the compound of formula (Ic)



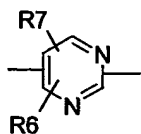
wherein all symbols are as defined earlier.

5. A process for the preparation of novel pyrimidine derivatives of the formula (I)

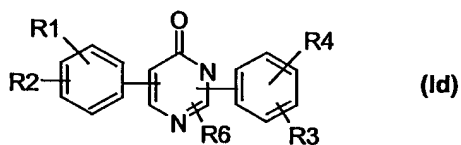


their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  may be same or different and independently represent hydrogen, hydroxy, nitro, nitroso,

formyl, azido, halo or substituted or unsubstituted groups selected from alkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; A represents pyrimidine derivative of the formula

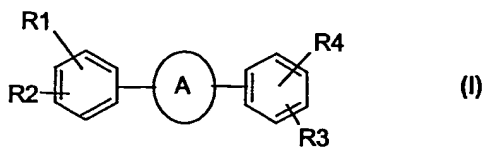


wherein any of R<sup>7</sup> represents halogen atom and R<sup>6</sup> represents hydrogen, nitro, nitroso, formyl, azido, halo, or substituted or unsubstituted groups selected from alkyl, alkoxy, acyl, cycloalkyl, haloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; the pyrimidine group may be attached to the phenyl through carbon or nitrogen atom; comprising converting the compound of formula (Id)



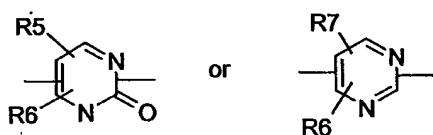
wherein R<sup>6</sup> is as defined above.

6. A process for the preparation of novel pyrimidine derivatives of the formula (I)

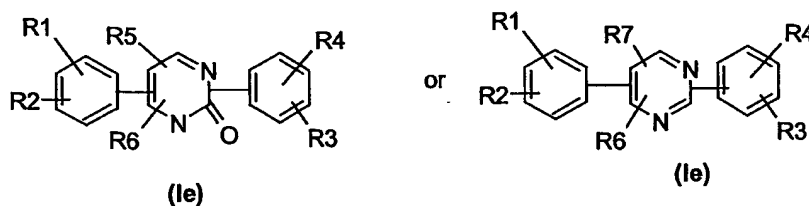


their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  may be same or different and independently represent hydrogen, hydroxy, nitro, nitroso, formyl, azido, halo or substituted or unsubstituted groups selected from alkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; A represents pyrimidine derivative of the formula

wherein A represents

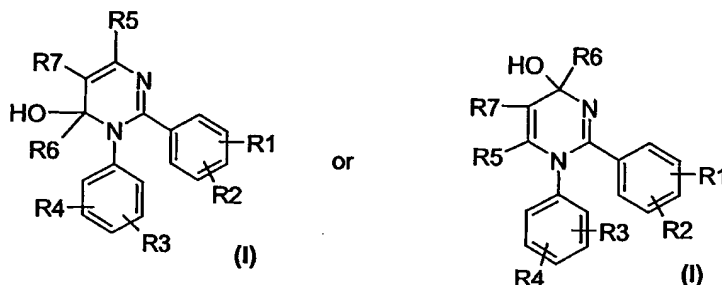


wherein  $R^6$  represents azido, hydrazine or hydrazine derivatives,  $R^5$  and  $R^7$  are same or different and represent hydrogen, nitro, nitroso, formyl, azido, halo, or substituted or unsubstituted groups selected from alkyl, alkoxy, acyl, cycloalkyl, haloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; the pyrimidine group may be attached to the phenyl through carbon or nitrogen atom; comprising converting the compound of formula (Ie)

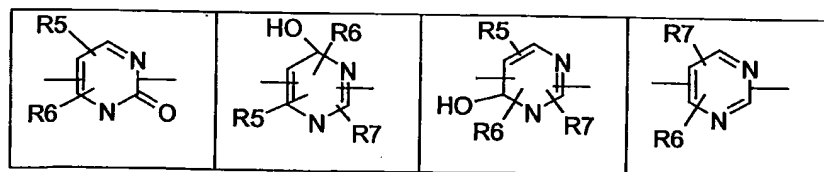


wherein  $R^6$  represents halogen atom and all other symbols are as defined above.

7. A process for the preparation of novel pyrimidine derivatives of the formula (I)

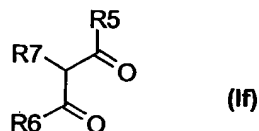


their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> may be same or different and independently represent hydrogen, hydroxy, nitro, nitroso, formyl, azido, halo or substituted or unsubstituted groups selected from alkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; A represents pyrimidine derivative of the formula

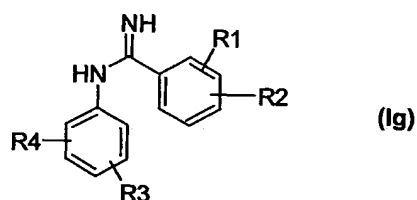


wherein R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, may be same or different and represent, hydrogen, nitro, nitroso, formyl, azido, halo, or substituted or unsubstituted groups selected from alkyl, alkoxy, acyl, cycloalkyl, haloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl,

carboxylic acid or its derivatives; which comprises reacting a compound of the formula (If)

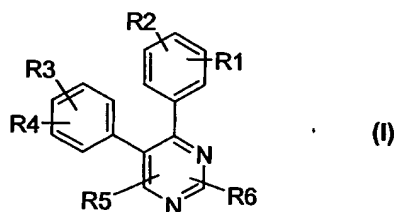


where all symbols are as defined above with a compound of formula (Ig)



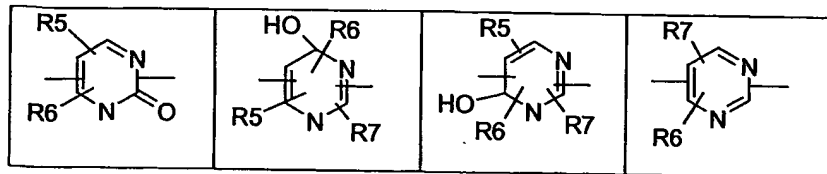
where all symbols are as defined above.

8. A process for the preparation of novel pyrimidine derivatives of the formula (I)



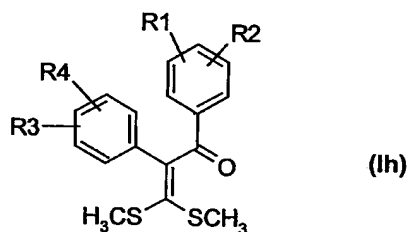
their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> may be same or different and independently represent hydrogen, hydroxy, nitro, nitroso, formyl, azido, halo or substituted or unsubstituted groups selected from alkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; A represents pyrimidine derivative of the formula



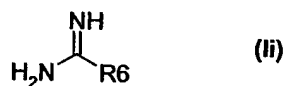


wherein  $R_5$ ,  $R_6$ , are same or different and represent, hydrogen, nitro, nitroso, formyl, azido, halo, or substituted or unsubstituted groups selected from alkyl, alkoxy, acyl, cycloalkyl, haloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; which comprises :

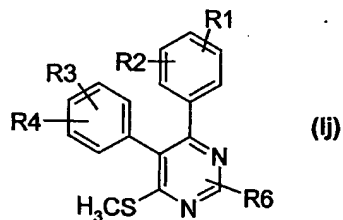
i) reacting a compound of formula (Ih)



where all symbols are as defined earlier with a compound of formula (Ii)



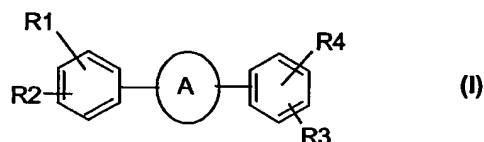
where  $R^6$  is as defined earlier to produce compound of formula (Ij)



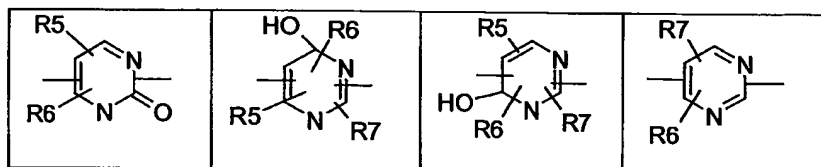
and

ii) converting the compound of formula (Ij) to produce compound of formula (I) where all symbols are as defined earlier by reacting with suitable nucleophilic reagent.

9. A process for the preparation of novel pyrimidine derivatives of the formula (I)



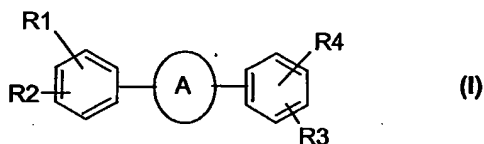
their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  may be same or different and independently represent hydrogen, hydroxy, nitro, nitroso, formyl, azido, halo or substituted or unsubstituted groups selected from alkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; A represents pyrimidine derivative of the formula



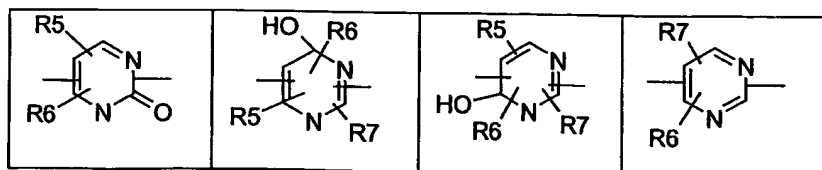
wherein any one of  $R_5$ ,  $R_6$ ,  $R_7$ , represent hydrazine derivatives and the other  $R_5$ ,  $R_6$ ,  $R_7$ , are same or different and represent, hydrogen, nitro, nitroso, formyl, azido, halo, or substituted or unsubstituted groups selected from alkyl, alkoxy, acyl, cycloalkyl, haloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, alkylthio,

arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; the pyrimidine group may be attached to the phenyl through carbon or nitrogen atom, prepared by reacting the compound of formula (I) wherein any one of  $R_5$ ,  $R_6$ ,  $R_7$  represent hydrazine.

10. A process for the preparation of novel pyrimidine derivatives of the formula (I)



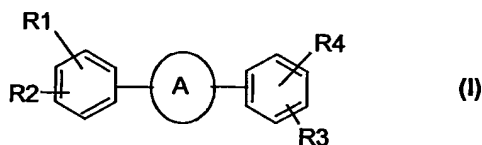
their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein any one of  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  represent alkylsulfonyl, alkylsulfinyl, aryl sulfinyl or arylsulfonyl and the other  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are same or different and independently represent hydrogen, hydroxy, nitro, nitroso, formyl, azido, halo or substituted or unsubstituted groups selected from alkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; A represents pyrimidine derivative of the formula



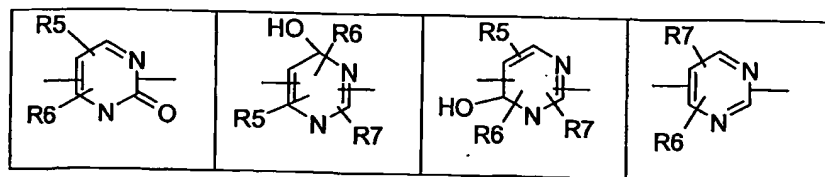
wherein any one of  $R_5$ ,  $R_6$ ,  $R_7$ , represent alkylsulfonyl, alkylsulfinyl, aryl sulfinyl or arylsulfonyl and the other  $R_5$ ,  $R_6$ ,  $R_7$ , are same or different and represent,

hydrogen, nitro, nitroso, formyl, azido, halo, or substituted or unsubstituted groups selected from alkyl, alkoxy, acyl, cycloalkyl, haloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; the pyrimidine group may be attached to the phenyl through carbon or nitrogen atom, prepared by reacting wherein the groups any of the groups  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$  represent alkylthio or arylthio and all other symbols are as defined above.

11. A process for the preparation of novel pyrimidine derivatives of the formula (I)

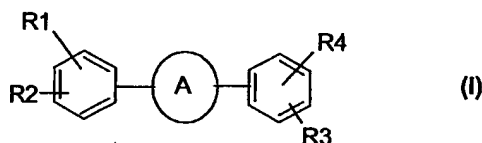


their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein any one of  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  represent sulfamoyl and the other  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are same or different and independently represent hydrogen, hydroxy, nitro, nitroso, formyl, azido, halo or substituted or unsubstituted groups selected from alkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; A represents pyrimidine derivative of the formula



wherein any one of  $R_5$ ,  $R_6$ ,  $R_7$ , represent sulfamoyl and the other  $R_5$ ,  $R_6$ ,  $R_7$ , are same or different and represent, hydrogen, nitro, nitroso, formyl, azido, halo, or substituted or unsubstituted groups selected from alkyl, alkoxy, acyl, cycloalkyl, haloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid or its derivatives; the pyrimidine group may be attached to the phenyl through carbon or nitrogen atom, prepared by reacting wherein the groups any of the groups  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$  represent alkylsulfonyl and all other symbols are as defined above.

12. A pharmaceutical composition, which comprises a compound of formula (I)



as defined in claim 1 and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

13. A pharmaceutical composition as claimed in claim 12, in the form of a tablet, capsule, powder, syrup, solution, aerosol or suspension.

14. A pharmaceutical composition which comprises a compound as claimed in claim 2 and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

15. A pharmaceutical composition as claimed in claim 12, in the form of a tablet, capsule, powder, syrup, solution, aerosol or suspension.

16. Use of a compound of formula (I) as claimed in claim 1, for the prophylaxis or treatment of rheumatoid arthritis; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; ischemic heart

disease, atherosclerosis, cancer, ischemic-induced cell damage, pancreatic  $\beta$  cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection. HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), and herpes zoster infection.

17. Use of a compound as claimed in claim 2, for the prophylaxis or treatment of rheumatoid arthritis; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; ischemic heart disease, atherosclerosis, cancer, ischemic-induced cell damage, pancreatic  $\beta$  cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection. HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), and herpes zoster infection.

18. Use of a composition as claimed in claim 12, for the prophylaxis or treatment of rheumatoid arthritis, Paget's disease, osteoporosis, multiple myeloma, uveitis, acute or chronic myelogenous leukemia, pancreatic  $\beta$  cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory

bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection.

19. Use of a compound of formula (I) as claimed in claim 1 for lowering plasma concentrations of either or both TNF- $\alpha$  and IL-1.
20. Use of a compound as claimed in claim 2 for lowering plasma concentrations of either or both TNF- $\alpha$  and IL-1.
21. Use of a composition as claimed in claim 12 for lowering plasma concentrations of either or both TNF- $\alpha$  and IL-1.
22. Use of a compound of formula (I) as claimed in claim 1 for lowering plasma concentrations of either or both IL-6 and IL-8.
23. Use of a compound as claimed in claim 2 for lowering plasma concentrations of either or both IL-6 and IL-8.
24. Use of a composition as claimed in claim 12 for lowering plasma concentrations of either or both IL-6 and IL-8.
25. Use of a compound of formula (I) as claimed in claim 1 for the prophylaxis or treatment of a pain disorder.
26. Use of a compound as claimed in claim 2 for the prophylaxis or treatment of a pain disorder.
27. Use of a composition as claimed in claim 12 for the prophylaxis or treatment of a pain disorder.

28. Use of a compound of formula (I) as claimed in claim 1 for decreasing prostaglandin production.
29. Use of a compound as claimed in claim 2 for decreasing prostaglandin production.
30. Use of a composition as claimed in claim 12 for decreasing prostaglandin production.
31. Use of a compound of formula (I) as claimed in claim 1 for decreasing cyclooxygenase enzyme activity.
32. Use of a compound according to claim 31, wherein the cyclooxygenase enzyme is COX-2 or COX-3.
33. Use of a compound as claimed in claim 2 for decreasing cyclooxygenase enzyme activity.
34. Use of a compound according to claim 33, wherein the cyclooxygenase enzyme is COX-2 or COX-3.



## INTERNATIONAL SEARCH REPORT

PCT/IB 03/02879

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/30 C07D239/48 C07D239/42 C07D239/36 A61K31/505  
A61P29/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 02513 A (FUJISAWA PHARMACEUTICAL CO) 20 February 1992 (1992-02-20) example 15	1,3-27
X	US 3 772 288 A (HARDTMANN G ET AL) 13 November 1973 (1973-11-13) claims 4,5; examples 1-10	1,3-27
X	US 4 438 117 A (CHERKOFISKY SAUL C) 20 March 1984 (1984-03-20) examples 9,10,14	1,3-27
X	EP 0 130 046 A (LILLY CO ELI) 2 January 1985 (1985-01-02) example 4; table 1	1,3-27



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 December 2003

Date of mailing of the international search report

11/12/2003

Name and mailing address of the ISA

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Authorized officer

Menegaki, F

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1(part),3(part)-27(part)

Present claims 1, 3-27 relate to an extremely large number of possible compounds. In fact, the-claims contain so many options and variables that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely Claim 2 and the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

PCT/IB 03/02879

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 16-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds/composition.
2. ☒ Claims Nos.: 1(part), 3(part)-27(part)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

PCT/IB 03/02879

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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US 3772288	A	13-11-1973	BE 759123 A1 BE 759176 A1 CA 962272 A1 DE 2056406 A1 DE 2056407 A1 FR 2077528 A5 FR 2073390 A1 GB 1328857 A NL 7016942 A NL 7016977 A OA 3525 A CH 539047 A DK 126042 B ES 385691 A1 JP 49011391 B	18-05-1971 19-05-1971 04-02-1975 27-05-1971 27-05-1971 29-10-1971 01-10-1971 05-09-1973 24-05-1971 24-05-1971 30-03-1971 15-07-1973 04-06-1973 01-10-1973 16-03-1974
US 4438117	A	20-03-1984	NONE	
EP 0130046	A	02-01-1985	US 4500533 A DK 300884 A EP 0130046 A1 GB 2142025 A , B GR 82683 A1 HU 34962 A2 JP 60013767 A KR 8601764 B1	19-02-1985 23-12-1984 02-01-1985 09-01-1985 17-05-1985 28-05-1985 24-01-1985 21-10-1986